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# SURGERY

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SURGERY

VOL. 41 JUNE, 1957 NO. 6

## Original Communications

# THE LOWER ESOPHAGUS LINED BY COLUMNAR EPITHELIUM

N. R. BARRETT, LONDON, ENGLAND

### DEFINITIONS

THE ideas discussed here are not based upon statistics nor upon a large collection of specimens; they are the results of thinking about a few unusual cases of esophageal disease. As such they may be rejected or modified in the light of future experiences. Some may be worried because I have changed my opinion relating to certain matters, but progress is not static and there is no subject which does not yield more knowledge as the depths are sounded.

This paper concerns a condition whose existence is denied by some, misunderstood by others, and ignored by the majority of surgeons. It has been called a variety of names which have confused the story because they have suggested incorrect etiologic explanations; congenital short esophagus, ectopic gastric mucosa, short esophagus, and the lower esophagus lined by gastric epithelium are but a few. At the present time the most accurate description is that it is a state in which the lower end of the esophagus is lined by columnar epithelium. This does not commit us to ideas which could be wrong, but it carries certain implications which must be clarified.

The literature about esophageal disorders is confused because common words have different meanings in the minds of different writers. To avoid misapprehensions on this score a few simple terms will be defined as to the sense in which they are used in this paper. The *esophagus* is the narrow passage through which food and drink pass from the pharynx to the stomach. *Gullet* is an alternative word which is useful because it has no exact anatomic significance. The *cardia* describes the mechanism (flap valve or whatever it be) which prevents reflux from the stomach into the esophagus. The word does not refer to the site at which the gullet widens out into the stomach nor to a hypothetical muscle sphincter which some believe separates the two.

Lecture given at the Mayo Clinic and at Professor Owen H. Wangensteen's Surgical Clinic at the University of Minnesota in Minneapolis, Minn., in November, 1956.

Received for publication Jan. 25, 1957.

This paper is based upon the proposition that the condition under discussion is importantly different from *sliding hiatal hernia.* The latter is an acquired deformity, which may be present at birth, in which a part of the stomach has migrated from below the esophageal hiatus into the mediastinum. The esophagus has in fact become, temporarily or permanently, short, and a narrow tube of true stomach is elevated in consequence. As the description of the condition under discussion proceeds, the anatomic and clinical differences between it and hiatus hernia with short esophagus should be clarified beyond doubt.

Allison[1-3] has said that sliding hiatal hernia and a lower esophagus lined by columnar epithelium often exist together in one and the same patient. In such a person the proximal alimentary canal would be constituted in this way: pharynx, esophagus lined by squamous epithelium, esophagus lined by columnar epithelium, sliding hiatal hernia, and stomach.

The novelty of this anomaly of the lower esophagus is denied by those who remind us that it has been recognized for half a century under the title of "islets of ectopic gastric mucosa in the esophagus." At the risk of tedium this point demands absolute definition.

According to the Oxford Dictionary the word "ectopic" means out of place. In this sense an inguinal hernia contains tissues which are out of place, but surgeons do not refer to these structures as being ectopic. The words "ectopic" and "heterotopic" describe islands of epithelium found in parts of the alimentary canal where they are unexpected. Before the turn of the century pathologists had described patches of gastric epithelium as occurring at almost all levels in the gut but particularly in Meckel's diverticula. These patches were prone to pathologic changes and it was assumed, though never proved, that similar changes could be invoked to explain any lesion of the esophagus involving columnar epithelium. This at least is the sense in which I interpret the early writings of authorities such as Chevalier Jackson.[9] In these writings the pith of the matter was overlooked in so far as the esophagus was concerned. We know now that the best reason for splitting these hairs is to distinguish between those conditions which allow acid or alkaline digestive juices to bathe unprotected squamous epithelium and those, on the other hand, which are harmless because the unusual cells secrete no ferments.

The fact is that columnar epithelium can appear in the gullet as it traverses the mediastinum in three entirely different circumstances. The first is a sliding hiatal hernia; the second is the condition described in this paper, namely, that in which the lower part of the gullet is lined by columnar epithelium extending upward for a long or a short distance above the esophagogastric junction; and the third is true islets of ectopic columnar epithelium.

It may be apt to summarize the facts about islets of ectopic gastric epithelium in the esophagus. Taylor has carefully examined and reviewed this problem. He defines ectopic epithelium as a state in which a portion of the normal mucous membrane is replaced by a mucous membrane foreign to the

part but normal to some other reach of the alimentary canal. Such anomalies are common and occur in two varieties, congenital which may be superficial or deep and acquired.

*Congenital superficial epithelial heterotopia* is a process of substitution of the epithelium only. Nothing deep to the muscularis mucosae is involved. In the esophagus this is a common occurrence. In 1904, Schridde[18] found islets of glandular tissue resembling cardiac gastric glands in 70 per cent of the bodies he examined. He stressed that the islets were situated in the postcricoid region and that they could generally be seen with the naked eye (varying in size from 1/8 to 3/4 inch in transverse diameter). They presented as smooth, velvet, depressed areas which were apt to be mistaken for erosions and were more often found on the back than the front of the gullet. He believed that they secreted gastric juice but that they were harmless because the ferments were neutralized by saliva. These findings were confirmed by others, notably Rector and Connerley[16] who, in 1,000 consecutive autopsies performed on children, found 89 examples of heterotopia in the esophagus. Twenty-six of the patches contained parietal cells but none had caused pathologic changes.

*Congenital deep epithelial heterotopia* involves the growth of epithelial structures in the esophagus deep to the muscularis mucosae and includes conditions such as gastric cysts and adenomyomatous tumors.

*The acquired heterotopias* are commonly found in the stomach and beyond and are manifest in the edges of healing ulcers (peptic, dysenteric, and tuberculous), ulcerative colitis, and other inflammations. They matter in the present discussion because if for any reason the squamous lining of the lower esophagus were to be destroyed it could, theoretically, be replaced by columnar cells. Moreover, the replacement could be patchy and simulate islets of heterotopia.

## THE PRESENT ANOMALY

When the lower esophagus is found to be lined by columnar cells, the abnormally placed mucous membrane extends upward from the esophagogastric junction in a continuous, unbroken sheet. There is no question of ectopic islets. The extent of the anomaly varies from a few centimeters to the upper esophagus. This deformity is not associated with or complicated by other anatomic changes: that is (1) the external appearances and the muscular anatomy of the stomach and the esophagus are normal; (2) there is no anatomic change in the mediastinum; (3) the blood supply from the aortic segmental arteries and the left gastric artery is normal; and (4) the crus of the diaphragm and the peritoneal reflections in the neighborhood of the hiatus are normal.

## THE ETIOLOGY

At present the explanation of this anomaly is not known. The following observations are suggestions which bear upon it.

*Comparative Anatomy.*—The mucous membrane of the esophagus and of the stomach varies in its distribution in different species of mammals. It is principally in the carnivora that the epithelium changes abruptly from squamous

to columnar precisely at the level of the "cardiac valve." And in this group the esophagus widens into the stomach at the same place as that at which the epithelium changes.

The anatomy of the mucous membrane of the foregut depends upon the food habits of the animal concerned. Those which have teeth in the mouth and which eat meat are arranged as we are; but in ruminants and species which are edentulous in the mouth, the stomach not only masticates the food but stores it before digestion.

Thus it comes about that in most vertebrates there is no "cardiac valve" mechanism and an important part of the stomach is lined by horny squamous epithelium. The extreme example is ornithorynchus (the duck-billed platypus) in which the squamous epithelium of the esophagus continues onward as far as the pylorus. But an important area of the stomachs of animals as widely different as the horse, the cow, the rat, and the rabbit is covered by squamous cells.

The points which are relevant to our discussion are these: (1) The precise limits of this or that epithelium is of no moment in most mammals in which a cardiac sphincter would be an unnecessary luxury. (2) This anomaly of the lower esophagus cannot be explained as a reversion to a more primitive zoologic type. (3) The tendency in the mammalian world is for squamous epithelium to continue onward toward the pylorus, not for columnar epithelium to grow up the esophagus.

*Histology of Human Specimens.*—Confusion has crept in again here, for although there is no doubt that in these cases the mucosa lining the lower esophagus looks, in every way, identical to the stomach (being velvety in texture, bluish in color, and raised in typical rugae), there are those who argue whether or not it is stomach.

The facts are these:

The thing which importantly distinguishes the stomach of a man from the esophagus is its mucosa. The mucosa of the stomach is formed of special tall columnar cells which are prolonged deeply into simple or branched tubules whose components have undergone further differentiation into cardiac, fundal, and pyloric glands. These glands secrete hydrochloric acid, mucus, pepsin, and secretin.

Functionally the columnar mucous membrane in these esophageal cases secretes little if any acid, pepsin, or secretin.

Histologically the upper part of the esophagus is normal and there is an obvious and abrupt transition between this and the unusual segment at the bottom. Just below this boundary, whose margin is corrugated, the columnar cells are flat and arranged in shallow, tubular glands amongst which lie mucus secreting units. There are no oxyntic cells and the structure of these glands resembles the normal deep esophageal glands.

Lower, in the esophagus the simple tubular crypts give place to more typical gastric mucous membrane. Scattered oxyntic cells appear. At any level in this abnormal segment, perfectly formed patches of squamous epithelium occur.

These findings, which are similar to those described by Allison and Johnstone,[3] suggest that the abnormal epithelium, despite its looks, does not function exactly as stomach and probably secretes little digestive juice.

*Embryology.*—Until recently differences of opinion have existed as to the development of the esophageal epithelium and of its glands in man. To elucidate these problems transverse sections of human embryos, at all stages in development between 3 mm. and 230 mm. C.R. lengths, were cut by Johns (1952).[10]

From the 3 to the 16 mm. stage the epithelium from one end of the gullet to the other is stratified *columnar* in type.

Between the 23 and 34 mm. stages it becomes two-layered and subsequently changes to multilayered although the cells remain columnar. This epithelium proliferates to such an extent that the lumen of the esophagus is actually, or nearly, obliterated and the channel is ultimately re-established by vacuolation. The vaculoles are largest above the level of the tracheal bifurcation and persist until the embryo is about 70 mm. long. Similar vacuolation occurs in the embryonic esophagus of the pig, rabbit, rat, and hedgehog.

After the 70 mm. stage, islets of ciliated columnar epithelium, which arise from the basal layer of the preceding stratified columnar lining, appear in the middle of the gullet; they extend, coalesce, and ultimately line the whole tube.

In the 130 mm. embryo the ciliated columnar lining is replaced by stratified squamous epithelium, and this change also begins in the middle reach of the esophagus and extends upward and downward. The last segment to lose its ciliated columnar epithelium is the upper end of the gullet, and traces of these cells have been described as persisting at birth.

During the development of a human embryo the sequence of changes in the epithelia which line the foregut might be arrested or deviated from normal. Thus it should not surprise us to find columnar, ciliated, transitional, or squamous epithelium anywhere between the mouth and the duodenum.

*Acquired Heterotopia.*—One of the facts which are difficult to explain is why this deformity always involves the lower esophagus. No specimen has as yet been described in which the whole of the gullet is lined by columnar cells. The explanation could be that if the cardiac valve of a normal person were to become incompetent and if the lower esophagus were, as a result, to be bathed for a long time by digestive gastric juice, the squamous epithelium could be eaten away and totally replaced by more quickly growing columnar cells. This concept might explain the site of the deformity, the fact that many cases occur in patients who have an incompetent cardia due to a sliding hiatal hernia, and the fact that many patients are elderly and have a history of heartburn dating back many years. But defects, produced experimentally in the squamous epithelium of the esophagus of the dogs, heal by squamous regeneration.

None of these suggestions smooth away all difficulties and the etiology remains open to speculation.

## PATHOLOGIC CHANGES

Surgeons who have studied the histology of specimens removed at operation have found that the greater part of the unusual epithelium consists of simple tubular glands which secrete mucus but which include few true gastric elements. There are some oxyntic cells at the lower end of most specimens and these may be situated proximal to the junction between the gullet and the stomach. Thus the abnormal segment may sometimes be subjected to the harmful effects of its own gastric juice; but in speculating about this point there are other factors concerned.

The junction between the squamous and columnar epithelia in these cases is generally situated at about 20 to 25 cm. from the incisor teeth and not just above the diaphragm as it is in most sliding hiatal hernias; and the higher up the gullet a lesion is the less the risk that the squamous epithelium will be digested because the surface is more adequately protected by saliva and mucus.

Is there, in these patients, a "cardiac valve" mechanism, and if so where is it? My observations suggest that two types of cases occur. The first is the patient who has the lower part of the gullet lined by columnar epithelium and no pathologic lesion at the esophagogastric junction. On a barium swallow and when examined radiologically, this individual has what appears to be a normal gullet. The "cardiac valve" is in its usual place and the mechanism does not permit reflux; that is, the "cardiac valve" is a long way below the level at which the change-over in the epithelium occurs, and between the valve and the change-over there is a segment of gullet lined by abnormal epithelium. The fact that a "cardiac valve" can behave normally in such cases indicates that the esophagogastric angle is more important to this function than the exact histology of the epithelium at the level of the valve.

The second is that described by Allison and Johnstone[3] who reported that in most of their patients the lesion was complicated by the presence of a typical sliding hiatal hernia below the abnormal mucous membrane. In these there was no "cardiac valve" and free reflux of gastric contents was usual. In the past these cases have been diagnosed as straightforward examples of sliding hiatal hernia. In both types a variety of different lesions can occur singly or in combination.

*Reflux Esophagitis.*—Esophagitis is not so commonly the presenting abnormality as it is in cases of sliding hiatal hernia, but it occurs and may be initiated by reflux of gastric contents or as a result of secretions from the oxyntic cells which exist in the lower esophagus. It could also be due to both factors operating simultaneously.

The various pathologic changes which have been found follow the pattern described by Allison.[1-3] The lesions may be superficial, involving only the squamous epithelium, or they take the form of ulcers and leukoplakia. The ulcers are generally situated at the point where the squamous epithelium ends and the lower margin of the defect abuts upon the columnar epithelium. Ulcers which are due to esophagitis do not perforate or cause massive bleeding by

eroding a large blood vessel, but they can cause anemia because of a persistent small loss of blood. In some circumstances the inflammation may spread more deeply than the mucous membrane.

*Esophageal Stricture.*—When this occurs low in the mediastinum as a complication of sliding hiatal hernia, the strictures are due to reflux esophagitis and are caused by dense fibrous tissue which permeates the muscular coats of the esophagus, occasions mediastinal adenitis, and fixes everything to the adjacent structures. A few strictures occur which are like a cord of string tied in the submucosa and, as Allison says, these can be shelled out locally without interrupting the continuity of the gullet. It is also stated that, upon occasion and particularly in children, ascending esophageal fibrosis can develop and occlude a long length of lumen.

I assume, but am not convinced, that when the lower esophagus is lined by columnar epithelium and when a stricture develops high in the mediastinum at the junction of the squamous and columnar elements, the processes described above can be operative. But the outstanding feature of the specimens we have examined to date is not principally scar; it is muscle hypertrophy. Starting at the level where the epithelium changes, there is a striking increase in the circular muscle of the gullet. This accretion tapers off below the stricture over a distance of 2 inches or more. Whatever may be its cause it is not comparable with the hypertrophy proximal to obstructions elsewhere because it is most accentuated at the level of and beyond the stricture. Histologically the hypertrophied muscle bundles look normal and are not importantly invaded by inflammatory cells. The appearance of the tissue contrasts strongly with the base of a typical peptic gastric ulcer. Inside the muscularis mucosae, which is usually intact, there is generally a layer of submucous fibrosis with ulceration of the luminal epithelium; and the whole mass, which feels at operation hard like a cancer, is adherent to the adjacent structures in the mediastinum. Another point is that the blood vessels which nourish the submucosa and mucosa pass inward from the surface of the esophagus and negotiate this thick layer of muscle. Many of these vessels are thrombosed in the specimens we have examined.

These details could be important for the following reasons:

These strictures are not simply composed of scar. In many the bulk of tissue is circular muscle fibers.

It is generally assumed that the sequence of events which initiates an esophageal stricture of this type is peptic digestion leading to inflammation; that is, the inflammation spreads from within, outward; and as a secondary effect it produces the appearance of muscle hypertrophy because the gullet is shortened like the belly of the biceps in contraction. This explanation does not satisfy me because, in these cases, the esophagus is not short. Could it be that an entirely different process is at work? Suppose for the sake of argument that in some instances the first thing to go wrong is hypertrophy of the muscle. We know that wherever in the body a muscular tube changes its nerve supply, as does the esophagus between its upper and lower reaches, at that place it is

likely to develop muscular disorders such as hypertrophy, leiomyomata, conditions of spasm, neurofibromata, and so forth. If there should prove to be a basis of reason in this thought, the possibilities of treating these strictures, assuming them to be a muscular anomaly aggravated by sepsis, would be different from current practice.

### ULCERATION

*Peptic Ulcer.*—Cases have been described of patients who have developed peptic ulcers in the abnormal segment of the lower esophagus. These ulcers have nothing in common with the shallow and transient esophageal erosions described above. They occur at a level below the change-over in the mucous membrane and they behave as do gastric ulcers in the stomach. Two kinds of peptic ulcer have been found.

*Acute peptic ulcers:* Acute peptic ulcers are not uncommon. It may be that these defects are the result of post-mortem changes in some instances, but they could be real ulcers. Their presence could account for some cases of unexplained hemoptysis. Allison has raised another interesting point. It is not known whether such an ulcer would heal by covering of columnar epithelium. It might heal by squamous metaplasia and if so, could account for the islets of squamous epithelium which have been found among the columnar cells. Such a speculation emphasizes the ever-recurring difficulty as to which lesions of the gullet are acquired and which are congenital.

*Chronic peptic ulcers:* Chronic peptic ulcers in the esophagus were described by Rokitansky, but the issue has been confused because it was formerly stated that they had arisen in isolated patches of ectopic gastric mucous membrane.

The differences between these ulcers and esophageal ulcers, on the one hand, and gastric ulcers, on the other, were first emphasized by Barrett,[4] in 1950, and for this reason the chronic peptic ulcer which complicates the lesion we are discussing and which is situated in what appears to be the gullet has been called Barrett's ulcer in the literature.

Barrett's ulcers are chronic gastric ulcers. They generally occur in middle-aged or elderly people and they invade and destroy the muscle coats of the esophagus. The adjacent tissues are edematous in life and as the ulcer penetrates through the wall of the gullet the mediastinal tissues become involved by fibrosis and inflammatory adenitis. The ulcer is liable to produce fatal hemorrhage by perforating a large blood vessel or mediastinal and pleural suppurations. Malignant change has also been described as having originated in such an ulcer, but the evidence is not conclusive.

The risk of a stricture forming is not great, because these ulcers grow in the line of the gullet and seldom involve the whole circumference. Thus the fairway is not usually obstructed and dysphagia, of which the patient may complain, is generally due to spasm above the lesion and to local edema. One may generalize and say that a benign stricture discovered in the lowest part of

the gullet is not likely to be due to a gastric ulcer. On the other hand, a stricture demonstrated at or above the aortic arch is almost certainly situated above an esophagus lined at its lower end with columnar epithelium.

Allison and Johnstone have stated that stenosis at the lower end of the gullet is not likely to be due to stenosis in connection with a Barrett's ulcer.

Carcinoma occurs immediately above the level of the change-over in the mucous membranes, in which case it is squamous in type and in the lower part of the esophagus when it is columnar. There are no special features which distinguish these lesions histologically from those growing in the normal gullet or stomach, but one important misconception needs correction. If a carcinoma starts at the normal anatomic esophagogastric junction and if it is columnar, it is difficult to say whether it has originated in an abnormality of the type under discussion in this paper or whether it is an example of a direct upward extension of a gastric cancer into the esophagus. The point is of academic interest at the level of the diaphragm but if a columnar cell growth is discovered at the level of the arch of the aorta, how is one to interpret this finding? In the past it has been said that the inference in such a case is that a gastric cancer has grown up the gullet from the level of the diaphragm. If this were always true the prognosis as regards resection would be hopeless because of the extent of the tumor. But it is seldom true. The usual explanation of such a finding is that the patient has developed a columnar cell cancer de novo in columnar esophageal mucosa. Some of these columnar cell cancers are localized and favorable for resection. The explanation that a columnar growth could have originated in an esophageal mucous gland is possible but has not been substantiated by an actual specimen. To prove this contention would involve demonstrating a columnar cell cancer entirely surrounded by squamous epithelium, and Carrie[7] has likened this to the unicorn which many have described but only one has seen.

## DIAGNOSIS

When the lower part of the gullet is lined by columnar epithelium, the patient will have no signs or symptoms unless a pathologic lesion is present. In such a one, a barium swallow would not reveal an abnormality either in the part which is assumed to be normal gullet or in the stomach. That is, columnar epithelium in the lower esophagus does not affect normal peristalsis or cast a typical shadow of rugae in roentgenograms.

The diagnosis will only be made when a pathologic process has been added to the abnormality of the mucous membrane.

The symptoms of esophagitis and its complications are the same as those which occur when this process is due to a sliding hiatal hernia, except that the pain is often felt higher up in the thorax and referred to the middle of the sternum. Dysphagia and regurgitation of food and saliva with mucus are common, and anemia due to slow bleeding is a feature.

The symptoms due to Barrett's ulcer or to its complications are not specific, but the pain is more likely to be related to the taking of food than to the effects of posture. It is not usually associated with belching of wind, heartburn, or abdominal discomfort. These patients may complain of a severe, boring pain

localized to the back if fixation to the aorta is occurring. If, on the other hand, there is a perforation into the mediastinum, the signs and symptoms mimic those which are characteristic of a perforated gastric ulcer in the peritoneal cavity. I have had experience of a case in which the ulcer caused, at first, a pericardial effusion and, later, death due to suppurative pericarditis. If a major blood vessel such as the aorta is eroded, the patient dies of massive hemorrhage. Loss of weight is a common complaint, and symptoms such as dysphagia are often of long duration. There may be periods of remission in which it is possible that a measure of healing has occurred, or spasm and edema may have subsided for the time being. In the first series of cases which I published, the patients had died as a result of the complications caused by their ulcers. None had been diagnosed correctly or treated in life.

*Radiologic Findings.*—Johnstone has described the radiologic findings when the lower esophagus is lined by columnar epithelium. He has emphasized that, unless a pathologic lesion is present in the esophagus, there is no special pattern caused by the columnar mucosal folds which suggests the diagnosis. The superficial lesions due to esophagitis cannot be seen and peristalsis is not abnormal. A benign stricture at the level of the aortic arch should suggest that the lower esophagus is lined by columnar epithelium because sliding hiatal hernias are not usually as large as this.

The "cardiac valve" mechanism in these cases will be incompetent if a hiatal hernia is present as well; but if it is not, there will probably be a mechanism which prevents reflux situated at the expected place, that is, below the diaphragm where the gullet appears to enter the stomach. These cases lend support to the proposition that the most important single factor in competence or otherwise of the "cardiac valve" is the angle at which the gullet enters the stomach. I have had 2 patients who, in spite of symptoms, were at first thought to have nothing abnormal because a competent cardia was seen in the usual place below the diaphragm. Both had gullets lined with columnar epithelium at the lower ends and esophagitis at the level of the aortic arch.

If a Barrett's ulcer is present in the lower part of the gullet, Johnstone believes that a correct diagnosis can generally be made with a barium swallow. He says, "When a deep ulcer crater can be demonstrated close to the cardia, there is strong presumptive evidence of its gastric origin. Such craters may be more than a centimeter in diameter. The walls are clear-cut, and in one case terracing was observed. Undermining of the margins has also been seen, but the edges appear regular and smooth. The crater is usually single, but in two instances a second crater has been found. . . . They are more often on the posterior or the posterolateral wall, and they tend to spread longitudinally rather than to encircle the lumen. In some the crater lies in the stenotic segment, but in others the lumen is scarcely narrowed and there is little obstruction. Periesophageal infiltration is not uncommon, and soft tissue shadows may be seen at the base of the ulcer." It is not always possible to distinguish radiologically between such an ulcer and a carcinoma.

*Esophagoscopy.*—Esophagoscopy is an essential preoperative investigation in all patients suffering from disease in the esophagus.

The diagnosis should be suspected if the change-over of the mucous membrane is found at a high level. As the epithelial transition is sharp, there should be no difficulty in marking its point unless there is local inflammation. If there is a doubt, pinch biopsies will settle the matter. In most of my cases the change has been at about 20 cm. from the incisor teeth, and this is higher than one expects it to be if the diagnosis is a sliding hiatal hernia.

A fact which suggests that the lower part of the gullet is lined by columnar epithelium is that the level at which the change-over of the epithelium occurs at endoscopy does not tally with the observed level of the cardiac valve mechanism radiologically.

The diagnosis is clinched if columnar epithelium is found above a pathologic lesion in the gullet. If the patient has a stricture at the esophagogastric junction, the radiologist is likely to call it a carcinoma and the fixity of the parts may suggest the same mistake to the endoscopist even though a negative biopsy has been obtained. The moral of this is that if a good piece of tissue has been obtained for biopsy and if the histologic report is against carcinoma, the possibility of a benign stricture should be entertained. Such strictures occur at all levels in patients who have never swallowed caustics.

The diagnosis of Barrett's ulcer at endoscopy is difficult not only because these ulcers often develop beyond an esophageal stricture but because, through an esophagoscope, they look like carcinoma.

*Thoracotomy.*—In some cases the diagnosis will not be confirmed until the structures in the lower mediastinum and in relation to the right crus of the diaphragm which forms the esophageal hiatus can be inspected at thoracotomy. The presence or absence of a peritoneal sac and the anatomy of the hiatus and of the left gastric artery are the deciding factors.

## TREATMENT

The lower esophagus lined by columnar epithelium has not been recognized long enough for anybody to be dogmatic about treatment. The following observations represent ideas rather than techniques of proved value.

It is reasonable to inquire what is the practical importance of being able to distinguish between a gullet partially lined by columnar epithelium and a sliding hiatal hernia? Both produce similar diseases and all one need know is that there are two conditions which may be different in origin, but which apparently result in the same defects. It is possible to make a case against this argument.

1. In sliding hiatal hernia the abnormal segment is a part of the true stomach. In this condition it is neither true stomach nor esophagus. How it may behave physiologically and pathologically is impossible to predict.

2. When the lower part of the gullet is lined by columnar epithelium the "cardiac valve" (if one exists) lies beyond the point where the epithelia change. After a sliding hiatal hernia has been reduced, the "cardiac valve" and the change-over in the epithelia correspond in level.

3. In sliding hiatal hernia, competence of the "cardiac valve" is attained by restoring the parts to their normal anatomic positions. Symptoms due to the abnormality under consideration cannot be cured in this simple way because there is no hernia to reduce and because the inflammation in the gullet is not always due to incompetence at the "cardiac valve."

4. The strictures, which occur as a result of the lower gullet being lined with columnar epithelium, are situated higher in the mediastinum than those due to a sliding hiatal hernia. This increases the technical difficulties of reconstituting the alimentary canal after excision.

5. Barrett's ulcer is rare as a complication of sliding hiatal hernia. But peptic ulcers occur in paraesophageal or rolling hernias. It is relatively common if the lower part of the gullet is lined by columnar epithelium, and its presence raises difficult problems of treatment.

6. It is probable that the majority of columnar cell carcinomas arising in the gullet (as opposed to the cardiac end of the stomach) grow from a segment whose lining is abnormal. The treatment of cases of this type has not been specifically considered by surgeons as yet. The prognosis in relation to radiotherapy and excision may not be the same as it is when the growth is squamous or truly gastric in origin.

## Various contingencies arise, some of which will be discussed:

1. The patient complains of heartburn and on investigation the barium swallow is normal. No esophagitis is found at esophagoscopy, but the lower esophagus is lined by columnar epithelium.

In such circumstances I would tend to assume that the secretions from the lower part of the gullet were not the cause of the symptom and that the heartburn was due to intermittent reflux from the stomach. If medical measures did not produce relief, the object of performing an operation would be to improve the competence of the "cardiac valve," and the presence of the abnormal epithelium in the gullet could be ignored. Thus, some operation such as that advocated by Lortat Jacobs designed to accentuate the esophagogastric angle might be tried.

2. The patient complains of heartburn and has esophagitis above a stretch of gullet lined by columnar cells.

This could be due to reflux of secretions from the stomach or to secretion from oxyntic cells in the abnormal epithelium of the gullet. Hence, if an operation is to be performed, the lower end of the gullet must be separated from the zone of esophagitis. In practice this means resecting the gullet between the inflamed area of squamous epithelium and the stomach. The chief difficulty of this operation is to know how best to reconstitute the alimentary canal.

3. The patient has dysphagia due to a benign stricture at the change-over of the epithelia.

The best treatment of these cases is open to question because, as has been indicated above, there are a variety of different causes of esophageal obstruction which are all called strictures, and there is no accurate clinical way of deciding which is which preoperatively. For instance if the semblance of a permanent stricture is produced by spasm and edema due to inflammation or digestion of the mucosa, it might be reasonable to treat the patient medically, to allay the inflammation by using cortisone, to quiet the spasm with appropriate drugs, and perhaps to dilate the constriction through an endoscope. If the stricture is due to a localized submucous ring of fibrous tissue, Allison tells us that the ring can be excised and the parts returned to normal. If it is predominantly caused by hypertrophy of the smooth, circular, muscle fibers, some operation of the type devised by Rammstedt for pyloric stenosis might suffice. But if the stricture is principally due to fibrous tissue, one may regard the matter in the way Wangensteen[25] does and advocate subtotal gastric resection and pyloroplasty with subsequent dilatations of the stricture or take the view that nothing short of excision of the stricture itself is adequate to the occasion.

Whenever a stricture of the type we are considering is excised, the details of how to restore continuity arise. Morris[13] recommended end-to-end anastomosis of the esophagus as the simplest solution. Sweet and his associates[21] agreed with Valdoni[23] and have preferred esophagogastrostomy, while Ellis[8] has devised an operation in which he removes the stricture and the lower esophagus, divides the vagi, excises the pyloric half of the stomach, and re-establishes continuity by anastomosing the esophagus to a tube of stomach fashioned from the fundus and anastomosed at the other end to the duodenum. It is obvious that the parts must be amenable to surgery if they can sustain these various attacks.

In the United Kingdom, surgeons such as Allison, Brain, Davidson, myself, and others at first preferred esophagojejunostomy as a solution to the problem, but during the last 3 or 4 years we have been performing esophagojejunogastrostomy with improved clinical results. Merendino and Dillard[11] have shown that in experimental animals the free loop of jejunum interposed in this operation between the esophagus and the stomach is not subject to digestion from gastric juice, that it retains its peristalsis, and that it acts in some measure as a barrier against reflux.

In heralding this "new" operation let us remember that, before 1900, Tavel of Berne suggested using an isolated segment of small bowel to perform a gastrostomy because the transplant retained its peristalsis and prevented leakage. This observation was confirmed by Jean Charles Roux[17] who based his operation of gastroenterostomy en Y upon it, and in 1907, published his technique for by-passing a stricture of the esophagus in a child by using a free loop of jejunum in which arterial arcades had been so divided that the intestine reached from the neck to the stomach.

4. The patient has a Barrett's ulcer.

Surgical treatment is eventually essential in these cases but not before every effort has been made to establish temporary healing. Bed rest and a jejunostomy for feeding are good preliminaries. These ulcers probably behave like gastric ulcers and some can be induced to heal. As they heal, the edema in the surrounding tissues subsides and a patient who has complained of dysphagia may swallow again. To operate before taking these precautions is to invite technical difficulties. There is no information as to whether an ulcer which has healed will remain quiescent, and the feeling at the moment is that it should be removed. To achieve this the lower part of the gullet must be mobilized and the mass of inflammatory tissue around the ulcer itself makes this step difficult and, sometimes, dangerous. Before dissecting the gullet away from the aorta, the latter should be mobilized above and below the ulcer so that it can be temporarily clamped if serious bleeding should occur. After the lower part of the esophagus has been freed, this must be excised and the continuity of the alimentary canal restored.

5. The patient has a combination of pathologic lesions.

In these circumstances there will seldom be any alternative but to resect the whole of the abnormal area; and, if a sliding hiatal hernia is present as well, this must be reduced in order to achieve a competent cardia or excised with the lower part of the gullet.

6. The patient has a columnar cell carcinoma in the esophagus.

If the growth is situated at the lower end and in proximity to the stomach, the treatment will be as advised by Allison,[1-3] Sweet,[21] Wangensteen,[24] or Tanner for carcinoma at the cardia. In many cases the most the surgeon can offer is that he can so arrange matters that the patient can swallow. There is no justification in opening the chest in such a case, finding the growth to be inoperable, and saying nothing can be done. Whatever is found the patient's dysphagia must be relieved. This at least can be done.

If the carcinoma is at the level of the aortic arch or higher, there is less experience to draw upon. Two points suggest themselves. It may be that some of these cases will respond to radiotherapy better than one hopes, and this kind of treatment could be a valuable preliminary to surgical excision. Such problems are, at this moment, being reviewed by Smithers.[19] The other point is a surgical one. What should one excise? The whole of the lower esophagus and most of the stomach and its mesenteries or, more simply, the growth and the tissues in its immediate neighborhood? Either operation could involve plastic procedures such as reconstruction of a bronchus and perhaps replacement of a segment of the gullet by a suitable graft. Morson[14] and others have discussed these problems.

## SUMMARY

It is suggested that the lesion under discussion should be called the lower esophagus lined by columnar epithelium, and that it is probably the result of a failure of the embryonic lining of the gullet to achieve normal maturity. The

differences between this condition and sliding hiatal hernia are underlined, and some of the reasons for distinguishing between the two are discussed. The pathologic conditions which complicate the anomaly are enumerated and the methods of diagnosis are described. The necessity for treatment and the various problems involved are recorded.

The present knowledge concerning the lesions associated with columnar epithelium in the gullet has come at the time when surgeons are beginning to feel that the pathology and treatment of esophagitis have been mastered. It may be that the importance of this new topic will be to stimulate research once again.

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# THE ADRENAL CORTICAL RESPONSE TO SURGERY

## II. Changes in Plasma and Urinary Corticosteroid Levels in Man

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IT HAS been well established that major surgery in man results in activation of the adrenal cortex. Furthermore, extensive evidence exists that an increase in adrenocortical activity contributes importantly to the metabolic response of patients to surgical trauma. Various direct and indirect indices of adrenal function have been employed in such studies. However, during recent years important advances in the methodology of adrenal hormone measurements have greatly improved the specificity and accuracy with which adrenal activity can be quantitatively evaluated. Moreover, additional procedures now available permit the separate measurement in both blood and urine of free, active corticosteroid hormones and of certain conjugated, inactive products of corticosteroid metabolism. Since the level of active cortical hormone in the systemic circulation is always a resultant of hormone secretion, on the one hand, and of hormone disposal, on the other, it is obviously important to evaluate, in so far as possible, the changes occurring in hormone secretion, metabolism (conjugation), and excretion.

The studies reported here were undertaken in order to apply these newer methods to the study of the adrenocortical response evoked by major surgery. The following techniques were employed: (1) plasma free 17-hydroxycorticosteroids, predominantly cortisol (hydrocortisone) which is the major corticosteroid secreted by the human adrenal cortex; (2) those plasma conjugated 17-hydroxycorticosteroids which are derived from circulating free hormone by reduction and conjugation with glucuronic acid; and (3) urinary free and total (free plus conjugated) Porter-Silber chromogens (17-hydroxycorticoids), derived primarily from the renal excretion of (1) and (2). In addition, changes in these indices have also been measured, for comparison, in patients undergoing adrenocortical stimulation by administered adrenocorticotrophic hormone (ACTH) in the absence of operative trauma.

### MATERIALS AND METHODS

Studies have been carried out in the Colorado General Hospital on 19 patients; 12 underwent major surgery (Table I), and 7 received a standard intravenous infusion of ACTH (Table II). The surgical group included 9 men and 3 women ranging in age from 26 to 79 years. The duration of surgery

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TABLE I. CLINICAL DATA CONCERNING THE TWELVE PATIENTS UNDERGOING MAJOR SURGERY

| NO. | PATIENT | AGE | SEX | DIAGNOSIS AND CLINICAL CONDITION | OPERATION | ANESTHESIA | LENGTH OF OPERATION (MINUTES) | TRANSFUSIONS IN O. R. (UNITS) |
|---|---|---|---|---|---|---|---|---|
| 1. | D. A. | 29 | M | Aortic coarctation; good | Resection of coarctation | Thiopental nitrous oxide | 320 | 4.5 |
| 2. | L. R. | 45 | M | Papilloma of rectum; good | Wedge resection of lower sigmoid | Thiopental nitrous oxide | 180 | 1.0 |
| 3. | W. L. | 74 | M | Recurrent carcinoma of tongue; healed tbc; atrial fibrillation; 4 + depletion | Right suprahyoid and jaw dissection | Ether | 145 | 1.0 |
| 4. | E. McK. | 75 | M | Carcinoma of tongue; 4 + depletion | Radical neck dissection; tracheotomy | Ether | 195 | 3.0 |
| 5. | E. K. | 79 | M | Large bowel obstruction; 4 + depletion | Exploratory laparotomy | Ether | 135 | 1.0 |
| 6. | V. D. | 19 | M | Aortic coarctation; good | Resection of coarctation | Ether | 360 | 2.0 |
| 7. | J. M. | 43 | M | Bleeding duodenal ulcer; good | Subtotal gastrectomy | Ether | 220 | 1.0 |
| 8. | F. O. | 76 | M | Carcinoma of the stomach; good | Subtotal gastrectomy | Ether | 210 | 1.0 |
| 9. | E. W. | 60 | M | Carcinoma of stomach; gastrointestinal bleeding for 2 weeks; 4 + depletion | Exploratory laparotomy | Ether | 155 | 2.0 |
| 10. | T. G. | 48 | F | Pulmonary tbc; bronchoscopy day before; good | Partial left lung lobectomy | Ether | 250 | 3.0 |
| 11. | B. R. | 29 | F | Inactive pulmonary tbc; good | Right upper lobectomy | Ether | 220 | 3.0 |
| 12. | U. S. | 26 | F | Prolapsed uterus; good | Manchester repair | Ether | 120 | 4.0 |

from incision to closure ranged from 120 to 360 minutes (mean: 208 minutes). Anesthesia was ether in 10 cases and was induced with thiopental-plus-cyclopropane in 6 and with cyclopropane alone in 4. Two patients received thiopental–nitrous oxide throughout. All patients underwent one hour of carefully maintained anesthesia prior to incision as part of a study, previously reported,[25] of the effects of anesthesia alone. Patients in the ACTH group included 3 men and 4 women ranging in age from 21 to 59 years. These patients received 25 USP units of ACTH, dissolved in one liter of 5 per cent dextrose in water, infused intravenously over an 8-hour period.

All studies began at approximately 7:00 A.M. with the withdrawal of control plasma samples and the insertion of an indwelling urinary catheter. In

TABLE II. CLINICAL DATA CONCERNING THE SEVEN PATIENTS RECEIVING ACTH

| NO. | PATIENT | AGE | SEX | DIAGNOSIS AND CLINICAL CONDITION | OPERATION | DATE OF OPERATION | DATE OF ACTH |
|---|---|---|---|---|---|---|---|
| 34. | L. D. | 51 | F | Abdominal fistula; ulcerative colitis; 3 + depletion | Closure of fistula "pull-through" resection of distal colon | 7/24/56 | 8/15/56 |
| 35. | V. J. | 48 | F | Carcinoma of right breast with axillary metastases; good | Radical mastectomy | 8/1/56 | 8/15/56 |
| 36. | R. K. | 42 | M | Carcinoma of thyroid with metastases; pharyngeal cutaneous fistula; 2 + depletion | Tube grafting | 7/18/56 | 8/15/56 |
| 37. | J. H. | 53 | M | Inguinal hernia; 2 + depletion | None | — | 8/15/56 |
| 38. | R. S. | 56 | M | Inguinal hernia; loss of weight; 3 + depletion | Repair of hernia | 11/16/56 | 11/14/56 |
| 39. | M. L. | 21 | F | Graves's disease; good | Thyroidectomy | 11/20/56 | 11/14/56 |
| 40. | A. H. | 59 | F | Chronic cholecystitis, cholelithiasis, ventral hernia; good | Repair of hernia; cholecystectomy; choledochostomy | 11/26/56 | 11/14/56 |

the surgical patients subsequent samples were obtained after one hour of anesthesia, at the estimated mid-point of the operation, following closure, in the recovery room when consciousness was fully regained, and daily during the postoperative period. In the ACTH group, samples were withdrawn after 4 hours of infusion, one hour after the end of infusion, and daily thereafter. All blood samples were heparinized and centrifuged immediately, and the separated plasma was stored in the frozen state until analyzed. For urinary steroid determinations, control analyses were carried out on 2 or more 24-hour collections obtained prior to surgery or ACTH administration. On the morning of operation or of ACTH infusion, 3-hour samples were collected during the first 12 hours, followed by a single 12-hour collection. Thereafter, 24-hour samples were again obtained for approximately 6 days. Urine samples were collected without preservative on ice; aliquots were frozen and stored until analyses could be accomplished.

Plasma levels of free 17-hydroxycorticosteroids (17, 21-dihydroxy-20-ketosteroids) were measured by the method of Nelson and Samuels.[14] A recent modification suggested by Eik-Nes and Samuels[7] was used. In this modification, the chloroform extract of plasma is purified by benzene-water partitioning prior to column chromatography. This procedure reduces the content of nonspecific pigments and increases specificity for cortisol as judged by an improvement in the absorption curves of the Porter-Silber[17] sulfuric acid—phenylhydrazine reaction products. A series of 23 duplicate samples studied for the effect of benzene-water partitioning demonstrated that this modification resulted in somewhat lower plasma cortisol values than obtained by the original method, particularly when elevated levels were encountered. At normal levels little variation was observed between partitioned and nonpartitioned duplicate

samples. Consequently, the partitioned control levels in this study were in good agreement with the nonpartitioned normal levels obtained by other workers.[3, 22] When standard aqueous-alcohol solutions containing from 1 to 3 mcg. of cortisol were processed in the same manner as plasma, recovery averaged 71 per cent (range 61 to 90 per cent) with a standard error of ± 0.9 per cent. All plasma samples were corrected in terms of the recovery of 3 such standard solutions run in parallel. Using this correction, the recovery of 1 mcg. of cortisol added to 10 c.c. of plasma averaged 97 per cent (range: 85 to 107 per cent) in 15 analyses. Analytical results on experimental samples when run in duplicate were regularly reproducible to within 2 mcg. per 100 c.c. of plasma, when the concentration was 6 to 30 mcg. per 100 c.c.

Plasma conjugated 17-hydroxycorticosteroids were determined by a modification of the method of Bongiovanni,[5] modified by incorporation of the benzene-water partitioning as described above. This measures 17, 21-dihydroxy-20-ketosteroids which are conjugated with glucuronic acid. In this procedure, residual plasma remaining from the chloroform extraction of free 17-hydroxycorticosteroids is incubated with beta glucuronidase and re-extracted with chloroform. The extract is then treated as for the determination of free cortisol. The final extract, following column chromatography, is divided into 2 equal parts. The sulfuric acid reagent alone is added to one which serves as a blank, and the sulfuric acid-phenlyhydrazine reagent is added to the remaining portion for colorimetric measurement. Optical densities are determined on blanks, standards, and unknowns at 370, 410, and 450 mμ. Blank values are subtracted from the density of the corresponding unknown or standard. The final corticosteroid value is then calculated using the Allen[1] correction formula. The absorption curves for unknown conjugated samples, corrected for individual blanks, closely resemble curves obtained on pure tetrahydrocortisol which was employed as the standard. All plasma samples were corrected for an average recovery of 62 ± 2 per cent (range: 58 to 81 per cent) of 3 tetrahydrocortisol standards (1 to 3 mcg.) run in parallel. Using this correction, the recovery of 1 mcg. tetrahydrocortisol added to 10 c.c. of plasma residue has ranged from 88 to 110 per cent (average: 94 ± 1 per cent). Reproducibility of unknown plasma samples when run in duplicate fell within 4 mcg. per 100 c.c., in the range of 2 to 23 mcg. per 100 c.c.

Total urinary Porter-Silber chromogens (17-hydroxycorticoids) were measured by the method of Peterson and associates.[15, 16] In this procedure, 5 to 10 c.c. aliquots of urine are hydrolyzed with beta glucuronidase and extracted with dichloromethane, and the Porter-Silber reaction is applied to the final extract. Tetrahydrocortisol was employed as the standard. Recovery of standards added to water and run through the entire procedure averaged 95 ± 0.9 per cent (range: 85 to 105 per cent). Normal and preoperative levels ranged from 110 to 390 mcg. per hour (average: 284 mcg. per hour, equivalent to 6.8 mg. per 24 hours). Triplicate analyses of 10 urines showed an average variation of 30 mcg. per hour. A comparison of this procedure with the more time-consuming chromatographic method of

Sandberg and associates[20] was carried out. Since similar results were obtained with the two methods, the more rapid and convenient method of Peterson was used for these studies.

Free urinary Porter-Silber chromogens were measured by the Peterson method described above, using 50 to 100 c.c. of urine without prior hydrolysis. Determinations of free material in preoperative control samples ranged from 10 to 20 meg. per hour, approximately 5 per cent of the total urinary Porter-Silber chromogens.

Urinary creatinine was measured by the Bonsnes and Taussky[6] modification of the Jaffe reaction.

Statistical tests for significance were based on the difference in means, divided by the pooled sum of squares for each group, assuming the variance to be homogenous. The probability that a result was due to chance was determined by Fisher's table.[9]

All charts show a progression of plasma or urinary corticosteroid levels (ordinate) in relation to time (abscissa). The abscissa shows the day of surgery in hours and the postoperative period in days. In addition, the shaded vertical columns divide the day of surgery into consecutive phases of the surgical experience of all patients: anesthesia, mid-surgery, end of surgery, and recovery. Within each phase, plasma 17-hydroxycorticosteroid concentrations are plotted against the abscissa in terms of the actual time-course of individual patients. Each column defines the limits of variability in time, for the entire group, for that phase. Since there is no overlap, this permits the computation of mean levels for each phase. For example, mid-surgery for all patients in the group falls between 2 and 3½ hours from the preanesthesia sample. Thus, this time span defines the range of variability for all patients for mid-surgery, and means can be computed against both the abscissa and the ordinate.

All urine values are plotted at the mid-point, in time, of the collection periods shown on the abscissa.

## RESULTS

*Response to Surgery.—*

*Changes in plasma free 17-hydroxycorticosteroids:* Fig. 1 depicts the changes in plasma free 17-hydroxycorticosteroids. With the exception of 2 patients, control morning values were within the normal range (6 to 22 meg. per 100 c.c.) for this laboratory. This is in agreement with previous observations[25] that in the majority of patients the immediate preoperative level of plasma free 17-hydroxycorticosteroids is normal.

Although there was some quantitative variation within the group, the pattern of response was similar for all patients. A modest increase in free 17-hydroxycorticosteroid levels occurred during the preliminary hour of anesthesia in some patients but the mean change was not significant. Thereafter, almost all patients showed a prompt, significant elevation by mid-surgery, usually followed by a gradual additional rise throughout the remainder of surgery and

the early recovery period. In the majority of cases corticosteroid levels declined significantly by the first postoperative day, but a return to normal values did not occur until the second to sixth day after surgery.

*Changes in plasma conjugated 17-hydroxycorticosteroids:* Fig. 2 shows the changes in plasma corticosteroid conjugates. With the exception of one patient, preoperative values were within the normal range (2 to 22 mcg. per 100 c.c.) for this laboratory.

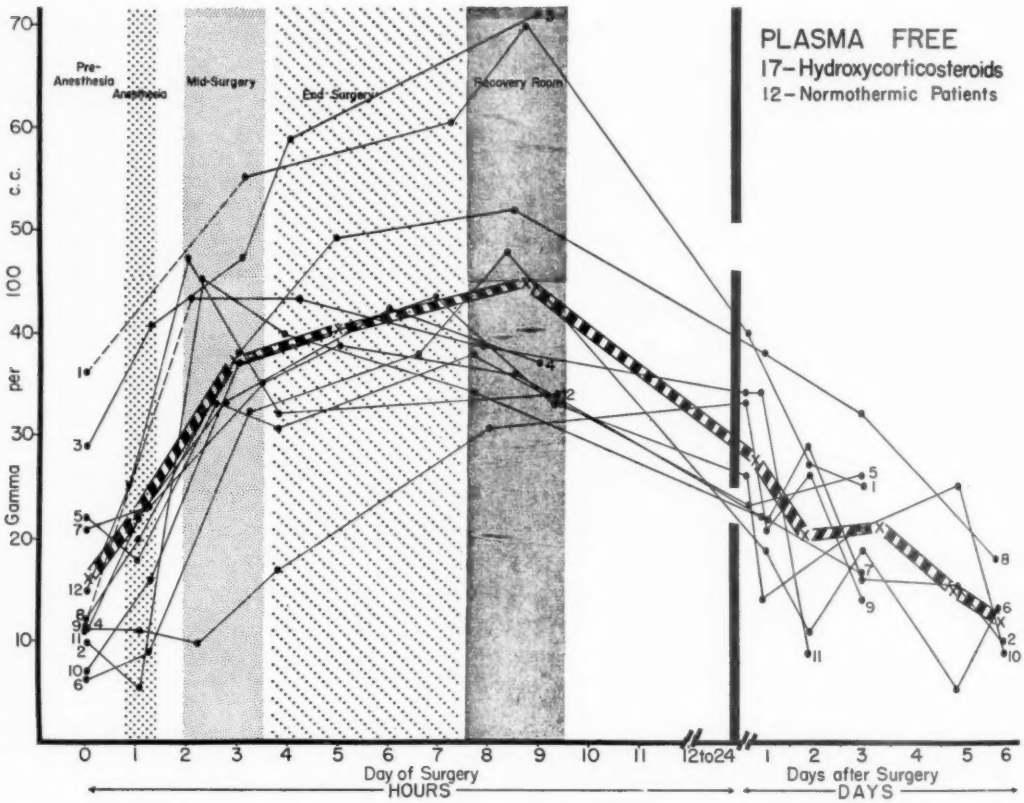


Fig. 1.—Response of plasma free 17-hydroxycorticosteroids to surgery. The abscissa denotes time in hours on the day of surgery and in days during the postoperative period. Consecutive phases of the surgical experience are plotted against the abscissa in the shaded vertical columns. The width of each column represents the total range, in time, for each episode for the entire group. Within this range, the concentration of plasma free corticosteroids, plotted against the ordinate, is also plotted against the time scale of the abscissa. The solid lines represent the course of individual patients and are numbered according to the data in Table I. Where an observation is missing the line becomes broken. The broad, heavy line shows mean values in terms of concentration in relation to time within each episode. All subsequent figures are similarly plotted.

In contrast to the changes in free 17-hydroxycorticosteroids, there were marked variations in the patterns of response. Five patients showed a moderate to marked rise in plasma levels, but in 4 patients very little change occurred. As might be anticipated, every patient who had an elevation in conjugate levels also showed a significant rise in free material; however, not every patient who had such a rise in free hormone showed an increase in conjugate levels. In those patients who exhibited significant increases in both free and conjugated steroids, the rise in conjugates was somewhat delayed

relative to the change in the free. In the postoperative period, some patients had returned to normal levels by the first day, while others had failed to return by the sixth day.

*Changes in urinary free and total Porter-Silber chromogens:* Changes in urinary corticosteroids are shown in Fig. 3. In addition, mean values for urine volume and urinary creatinine excretion are recorded. No significant changes in the output of creatinine occurred during or following operation. Urine volumes declined significantly during surgery.

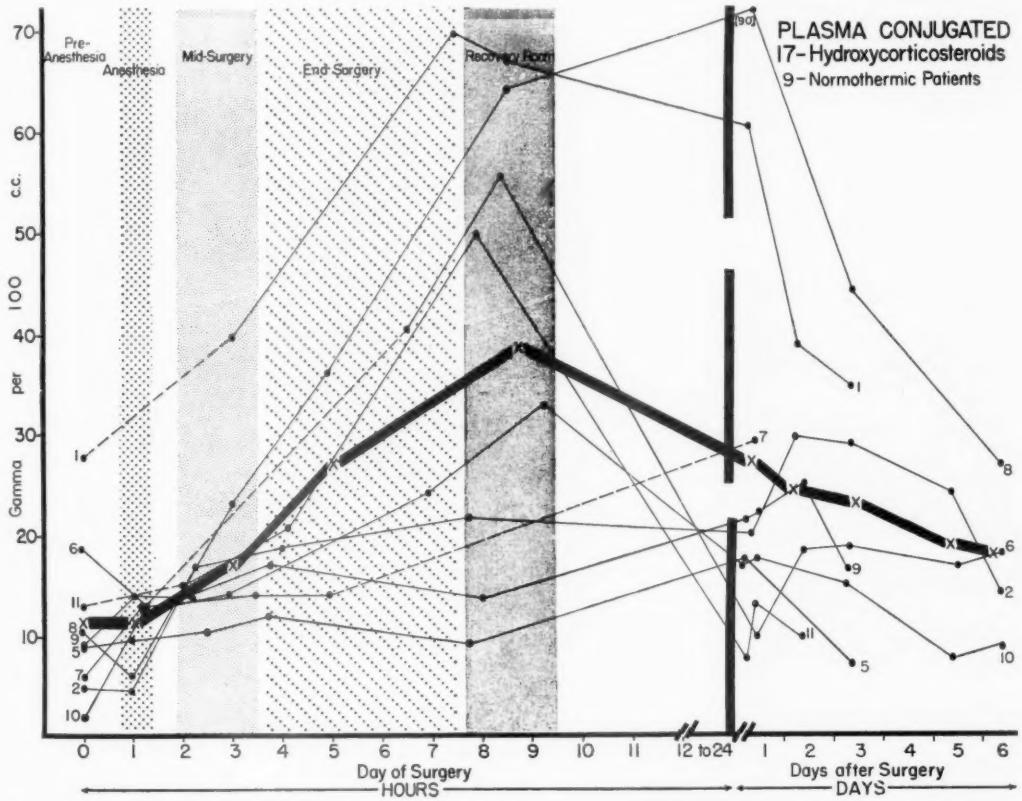


Fig. 2.—Response of plasma conjugated 17-hydroxycorticosteroids to surgery. The solid lines, representing individual patients, are numbered according to the data in Table II.

The excretion of free corticosteroids was measured in only 4 patients. A gradual steady increase occurred from a mean control value of 11 to a mean peak value of 138 mcg. per hour in the late afternoon of the day of surgery. Thereafter, the level gradually declined toward normal for several days.

Total corticosteroid output showed considerable variation within the group. These differences in response were accentuated by a temporary cessation in steroid excretion in 2 patients (Nos. 8 and 10), which was due to a transient period of severe oliguria. In both instances, it rose later when urine volume increased. In general, there was a gradual rise in urinary total Porter-Silber chromogens to peak values in the late afternoon or night of the operative day.

Postoperatively, a sharp decline in steroid output occurred, but levels comparable to control values were not reached until the third to sixth day after operation.

*Response to ACTH.—*

*Changes in plasma free 17-hydroxycorticosteroids:* The response of plasma free 17-hydroxycorticosteroids to an 8-hour intravenous infusion of ACTH at a dosage level known to induce maximal adrenocortical activation[19, 20] is shown in Fig. 4. A marked, rapid rise in plasma free corticosteroids was uniformly produced and the greater part of this change occurred during the first half of the infusion. Following the infusion, steroid levels fell rapidly and on the following day were back to control levels or below.

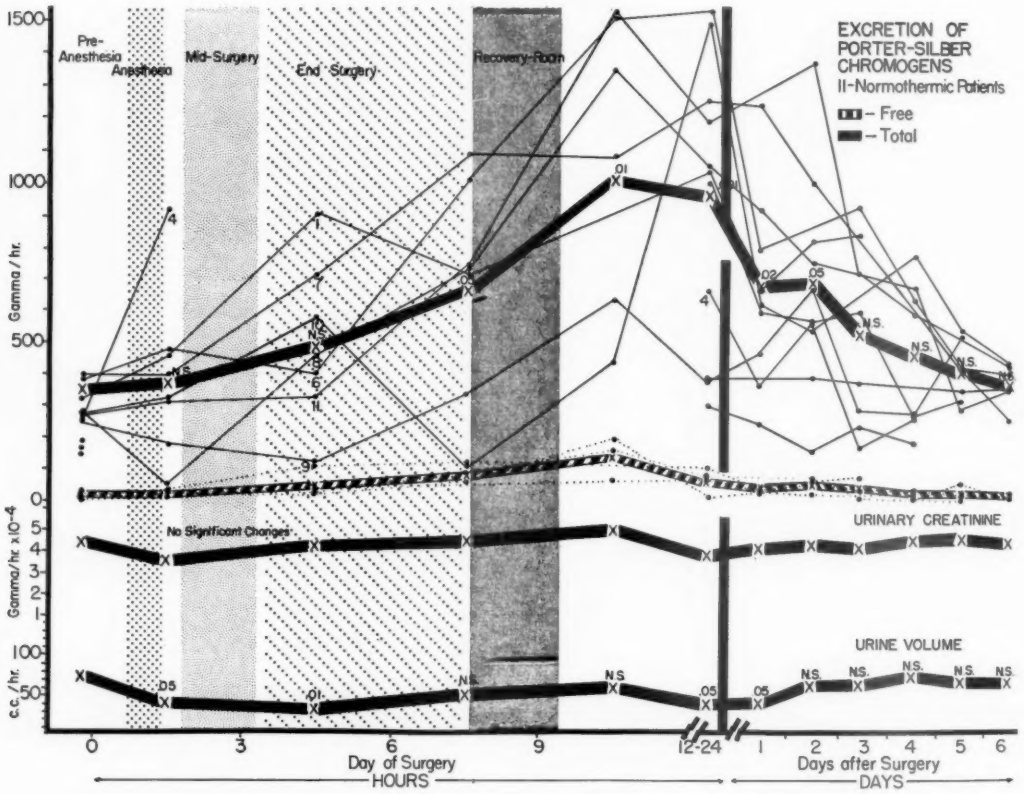


Fig. 3.—Response of urinary free and total Porter-Silber chromogens to surgery. Mean urine volume and urinary creatinine levels are also shown. The ordinate is calibrated in terms of excretion rates (units per hour). The abscissa is in terms of time and urine collection periods are indicated by the time intervals shown. All measurements are plotted against the abscissa at the mid-point, in time, of each collection period. Patients are numbered according to the data of Table I.

*Changes in plasma conjugated 17-hydroxycorticosteroids:* Changes in plasma conjugated 17-hydroxycorticosteroid levels following ACTH administration are shown in Fig. 5. The patterns of response were uniform. The increase in conjugate levels occurred more slowly than that of the free steroid, yet the highest mean level measured was the same for both indices. When ACTH administration was discontinued, conjugate values also returned rapidly to or below control levels.

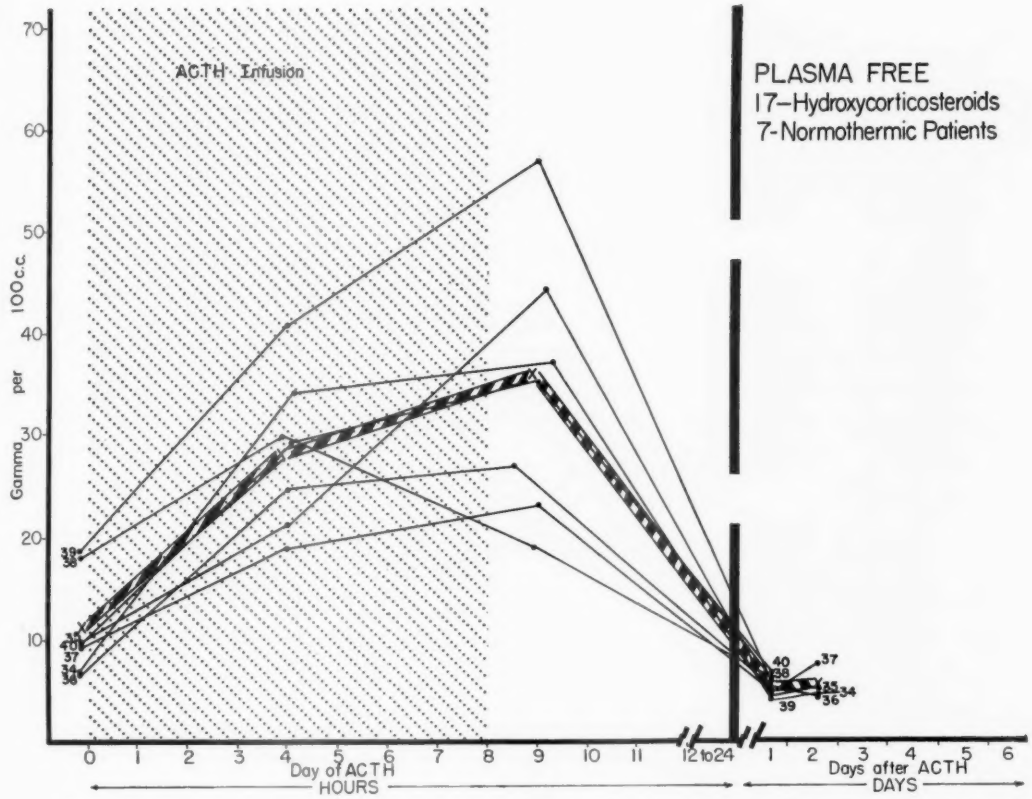


Fig. 4.—Response of plasma free 17-hydroxycorticosteroids to ACTH. ACTH (25 USP units) was infused intravenously over an 8-hour period. Patients are numbered in accordance with the data of Table II.

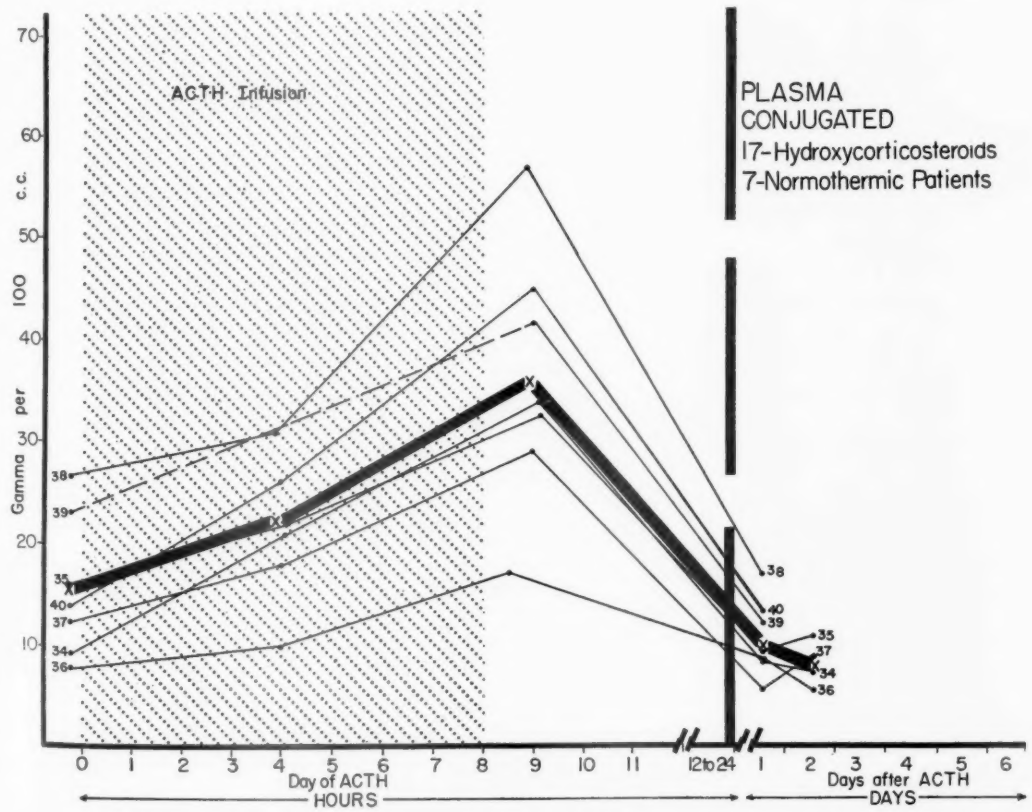


Fig. 5.—Response of plasma conjugated 17-hydroxycorticosteroids to ACTH.

*Changes in the urinary free and total Porter-Silber chromogens:* The patterns of steroid excretion illustrated in Fig. 6 are surprisingly uniform. Mean urine volumes and creatinine excretion are also shown and demonstrated no significant changes.

The urinary excretion of free Porter-Silber chromogens rose steadily throughout the infusion to a mean maximal value of 162 mcg. per hour and, thereafter, promptly declined. Total urinary corticosteroids also rose rapidly; maximal excretion rates were achieved in the 3-hour collection period immediately following the infusion of ACTH. By that night excretion was again equal to control values.

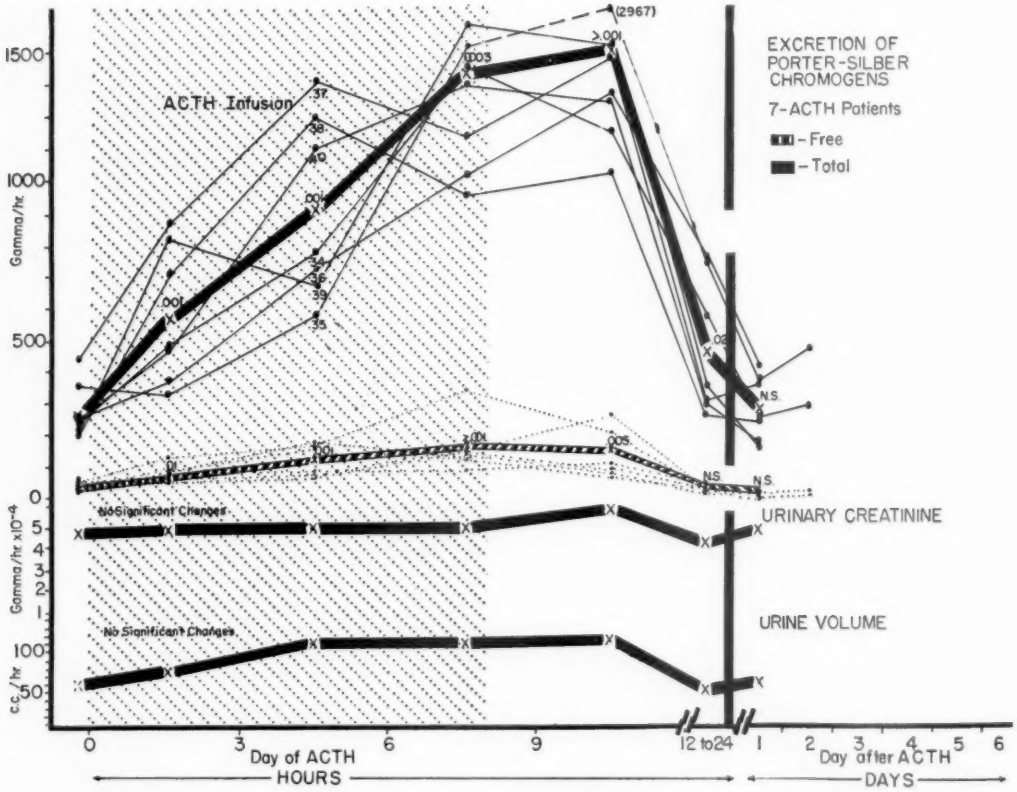


Fig. 6.—Response of urinary free and total Porter-Silber chromogens to ACTH.

*Comparison of the Responses to Surgery and to ACTH.—*

*Changes in plasma 17-hydroxycorticosteroids:* Mean curves of the changes in plasma free 17-hydroxycorticosteroids produced by surgery and by ACTH are shown in Figs. 1 and 4, respectively. It is evident that in both groups plasma levels of the free, active hormone rose rapidly and that there was no significant difference between the peak levels of response. However, the return to control levels occurred much more rapidly in the patients who received ACTH. This difference is undoubtedly attributable, at least in part, to the more prolonged stimulus of continuing tissue injury following major surgery.

The mean curves of plasma conjugate values in the two groups (Figs. 2 and 5) are also similar in terms of the initial response and the maximal levels

reached. Again, the return to control levels occurred more rapidly in the patients given ACTH. However, although the mean curves are similar, the major difference between the two groups in the behavior of plasma conjugates was the uniformity of individual response following ACTH administration as contrasted to the marked variability of the surgical group.

*Changes in urinary Porter-Silber chromogens:* Mean curves of the changes in free and total Porter-Silber chromogens are shown in Figs. 3 and 6. The mean maximal increases in excretion were not significantly different in the two groups. On the other hand, the initial rise in output occurred more slowly in the surgical group and returned to normal more slowly. As with the plasma conjugates, the individual patterns following ACTH were much more uniform than those following surgery.

## DISCUSSION

It is evident from these studies, in confirmation of previous reports by others,[10, 21, 23, 24] that major surgery induces a marked rise in the circulating level of free 17-hydroxycorticosteroids. Similarly, the increased excretion of urinary Porter-Silber chromogens observed in this study is in agreement with other reports.[13, 24] Of particular interest, however, are the changes in plasma conjugated 17-hydroxycorticosteroids since this index of the secretion and metabolism of cortical hormone has not been extensively studied.

The most striking aspect of the response in plasma conjugates was the marked variability observed. In some patients conjugate rose to remarkably high levels; in others essentially no change occurred. Since plasma conjugates are directly derived from circulating free hormone and since a significant elevation of free hormone occurred in every patient, it appears justifiable to conclude that marked differences in the rate of corticosteroid conjugation existed in these patients. An attempt to correlate these differences in the rate of conjugation with a number of clinical variables such as age, sex, underlying disease, general debility, type of anesthesia, or liver dysfunction was not rewarding. We have no specific explanation for these observed differences in the metabolism of free hormone during surgery in this group of patients.

The intravenous infusion of ACTH over an 8-hour period, in the dosage employed in these studies, produces maximal stimulation of the adrenal cortex with a rise of free plasma 17-hydroxycorticosteroids to levels approximately 3 to 5 times normal values[2, 8, 23] and a marked increase in the urinary excretion of free and total Porter-Silber chromogens.[11, 18, 20] In addition, plasma conjugates also rise significantly.[4, 12] The results of the present study, illustrating the simultaneous changes produced in all 4 indices by a standard ACTH infusion, are in agreement with the above findings. It is to be noted that the changes in a given index in time and intensity are basically similar in all patients.

It is generally believed that the rise in circulating cortisol induced by surgical stress results solely from an increase in endogenous ACTH secretion. Therefore, comparison of the corticosteroid changes elicited by surgery with those produced by exogenous ACTH administration is of interest. Plasma

free hormone levels in the two groups of patients were essentially similar both in the rate and the degree of change. Plasma conjugated corticosteroids showed far more variation in response in the group undergoing surgery. Urinary corticoids attained comparable peak levels in the two groups but the rate of increase was definitely slower in the surgical patients. Therefore, it would appear that two major differences between the course of events following surgery and that produced by an ACTH infusion are apparent. First, in association with surgery, the rate of conjugation of 17-hydroxycorticosteroids is diminished, at least in some patients. And, second, the excretion of corticosteroids is somewhat delayed during surgery in some patients.

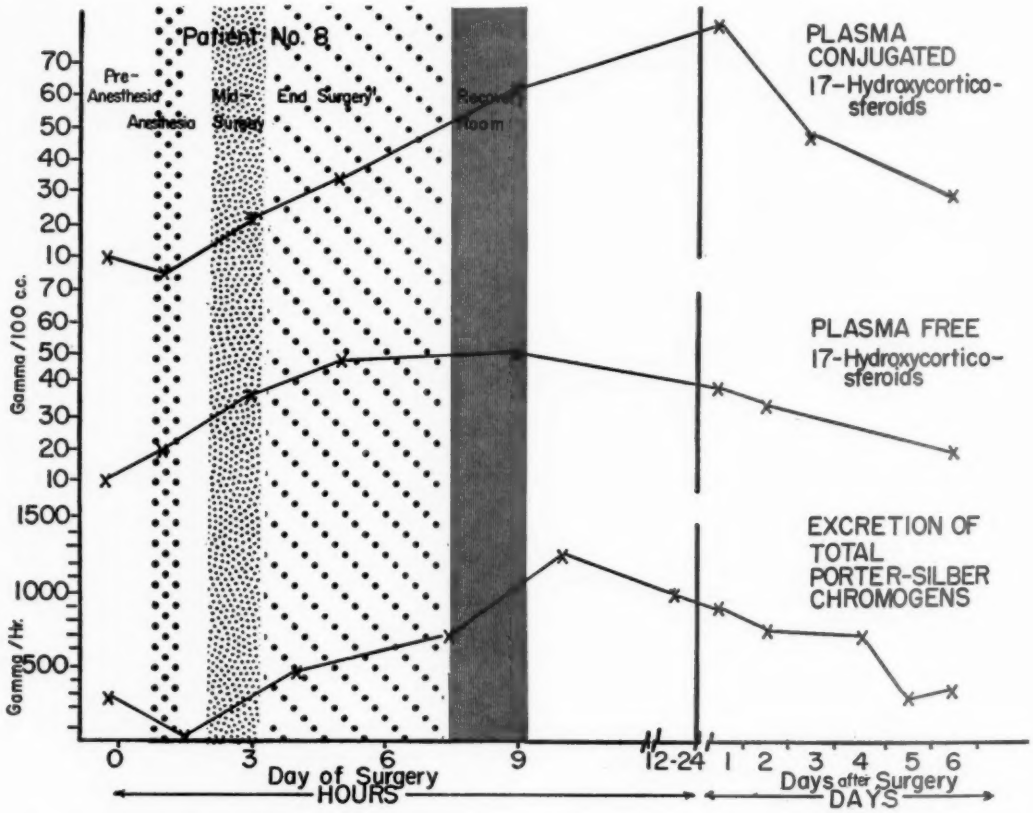


Fig. 7.—Response of plasma and urinary corticosteroids in a 76-year-old man undergoing gastric resection.

The direct demonstration in this study that the conjugation of cortisol proceeds at a minimal rate in some patients is in agreement with the previous conclusions of Sandberg and associates.[21] The latter group arrived at this opinion on the basis of the following observations: (1) even though plasma free 17-hydroxycorticosteroids rose during surgery to levels as great or greater than those achieved with a previous maximal ACTH stimulus, the readministration of ACTH following the completion of surgery produced a further significant increase in free hormone levels in some patients; and (2) the plasma disappearance rate of cortisol, infused intravenously during the immediate

postoperative phase, was sometimes materially delayed. In the present study, the measured plasma conjugated levels of several patients exemplify the response to surgery predicted by the above studies in that plasma free hormone levels rose significantly without an accompanying significant increase in plasma conjugates.

In contrast, however, several of our patients did not exhibit this pattern of response and, indeed, their response can hardly be interpreted as demonstrating a decrease in cortisol conjugation. Plasma conjugates in the latter patients rose to high levels. Furthermore, this rise could not be attributed to a failure in renal excretion since urinary total corticosteroids, after an initial moderate delay, also increased markedly. The following case illustrates this response pattern.

CASE 1.—F. O., Colorado General Hospital No. 77841, a 76-year-old man, was admitted to the hospital with a 2-month history of epigastric pain, anorexia, and a 10-pound weight loss. Radiologic examination revealed a large filling defect on the greater curvature of the stomach. Liver function studies were normal. A subtotal gastrectomy was performed and the diagnosis of carcinoma was confirmed. The postoperative course was satisfactory. His corticosteroid response is illustrated in Fig. 7.

It is to be noted that plasma free and conjugated 17-hydroxycorticosteroids and urinary total Porter-Silber chromogens in this patient all rose to high levels. In fact, the maximal level of each index considerably exceeded the mean response for the entire group. We find it difficult to interpret this pattern of response as indicating a significant decrease in conjugation.

While precise quantitative interpretation of the related events of corticosteroid secretion, conjugation, and excretion is difficult, the following statements concerning these processes during surgery appear justified on the basis of the present studies. Operative trauma produces pituitary-adrenocortical stimulation. The resulting acceleration of cortisol secretion by the cortex leads to a rapid rise in circulating free 17-hydroxycorticosteroids. The mechanisms of cortisol disposal are thereby stimulated. Two responses occur. In some patients, after a short delay, the level of conjugates increases, and, after another short delay, the urinary level of conjugated steroids rises sharply. All indices fall, at first rapidly and then more slowly, toward normal during the subsequent days. In others, the level of conjugates does not rise, and the subsequent elevation of urinary conjugate excretion is likewise less pronounced. All indices, including the free plasma level, are within normal ranges after several days. This latter response is probably due to suppression of conjugation in the liver rather than failure of excretion.

## SUMMARY

1. Free and conjugated 17-hydroxycorticosteroids in plasma and urine have been studied in 12 patients during and immediately following major surgery. These results have been compared with similar observations in 7 patients in whom adrenocortical stimulation was produced by the intravenous infusion of ACTH.

2. Both ACTH and extensive surgery produced a rapid and comparable rise in plasma free 17-hydroxycorticosteroids.

3. ACTH regularly produced an increase in plasma conjugated corticosteroids. This rise occurred somewhat later than the elevation in the level of free hormones.

4. Surgery produced a strikingly variable response in plasma conjugate levels in that a pronounced rise occurred in some patients, while a virtual absence of response occurred in others. Thus, cortisol conjugation is apparently impaired in some patients during surgery but not in others.

5. The renal excretion of Porter-Silber chromogens increased to comparable levels in both groups, but the response was somewhat delayed following surgery.

6. The postoperative return of all indices to normal is delayed in comparison to ACTH infusion.

We wish to express our appreciation to Dr. Robert W. Virtue, Chief of the Division of Anesthesiology, for his advice and cooperation, to Vera Drose for the preparation of the exacting figures, and to Anna Marie Lowe for careful technical assistance in this study.

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# STUDIES IN AMMONIA METABOLISM

## II. Ammonia Metabolism in Hemorrhagic Shock

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PROFOUND changes in blood ammonia concentrations[29] and protein metabolism[44] occur in hemorrhagic shock. Recent emphasis has been placed on the importance of gastrointestinal hemorrhage in precipitating ammonia intoxication and hepatic coma due both to the hepatic damage subsequent to a diminution in hepatic blood flow and to the increased ammonia load presented to the liver from the breakdown and absorption of blood within the intestine.[8, 40, 26]

This is a study of ammonia metabolism in hemorrhage and hemorrhagic shock in dogs to determine the source of portal bed ammonia in these conditions and to determine whether there is in fact an increase in ammonia production in the portal bed and to evaluate the capacity of the liver to clear ammonia from portal venous blood under these circumstances.

### Effect of Hemorrhage on Protein Metabolism

Normally two-thirds of the oxygen utilized by the liver arises from portal venous blood.[27] In hemorrhagic shock there is a marked diminution in portal blood flow[1] and in its oxygen content[13] resulting in hepatic anoxia[18, 43] and liver damage.[20, 24] Urea synthesis is diminished[10, 38] and deaminizing activity is suppressed[7, 12, 44] due perhaps to a circulating amino acid oxidase inhibitor.[7, 18] The cytochrome oxidase and the succinic dehydrogenase systems[34] are uninvolved, but some other system involving high-energy phosphate bonds[32] is primarily affected by shock. The result is an accumulation of urea but not of ammonia[2, 44] within the liver.

Following hemorrhage there is an increase in protein catabolism[11, 33] resulting in an increased peripheral blood concentration of amino acids,[10] of amino acid nitrogen,[9, 10, 19, 21, 24, 33, 35] and of nonprotein nitrogen,[37] but not of amide nitrogen[44] nor of urea.[2] Normally there is a significantly higher portal blood ammonia concentration[28] than elsewhere, but in shock, Nelson and Seligson[29] report an even greater rise both in the portal and peripheral blood.

Thermal trauma,[16, 19] tourniquet shock,[21] or pure hepatic anoxia[6] produce similar changes in protein and ammonia metabolism.

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These and other metabolic[36] and bacteriologic[14] products of disordered metabolism of the anoxic liver have been carefully studied to determine their pathogenic importance in shock or in hepatic coma. Recent revival[8, 25, 30, 39] of a long-standing interest[4, 23] in the problems of ammonia intoxication has suggested its importance as a toxic agent both in hepatic coma and profound ("irreversible") shock and is the reason for this study of ammonia production following hemorrhage.

## MATERIALS AND METHODS

A total of 27 adult mongrel dogs, weighing between 12 and 25 Kg. and maintained on a standard pressed cake kennel ration diet, were employed in this study.

Twenty-two dogs were subjected to hemorrhagic shock according to the method of Wiggers[41] The remaining 5 animals were bled stepwise until expiration. Bleeding was carried out by means of a 14 gauge cannula inserted proximally into a peripheral artery and leading into a graduated reservoir. Heparin was added in minimal quantities needed to prevent clotting. Arterial blood pressure was measured by connecting a cannula in the left femoral artery to a U-tube mercury manometer.

One shock experiment was performed in an unanesthetized animal previously prepared with portal and hepatic vein cannulae.[31] The remaining dogs were anesthetized with 35 mg. of pentobarbital per kilogram of body weight. Hepatic and portal blood samples were obtained in the one unanesthetized animal via cannulae. In the remaining animals the blood samples were obtained by direct venipuncture after laparotomy.

Blood ammonia concentrations were measured on freshly drawn (1 to 3 minute) heparinized blood samples according to a modification of the Conway microdiffusion technique.[5]

Blood volumes were determined by the Evans dye method.[17]

Two methods were used in measuring splanchnic blood flow. Bromsulphalein clearance technique[3, 31] giving values for total liver blood flow was employed in 23 animals.

Since it was desirable to determine portal blood flow separately in order to calculate splanchnic ammonia production, a direct measurement technique was devised and used in 7 experiments. This consisted of inserting a siliconized glass T-tube into a lateral slit in the portal vein. For 5- to 7-second periods the side arm was opened and the proximal end of the portal vein was occluded simultaneously to permit collection of portal blood in a graduated container. Immediately following measurement, the blood was restored to the general circulation.

In 3 animals relative sterilization of the intestinal tract was attained by the oral administration of a broad spectrum tetracycline antibiotic (Aureomycin) prior to induction of hemorrhagic shock (Fig. 4). Twenty-four hours prior to the experiment, these animals were placed on water and antibiotic alone by mouth. Although cultures of the intestinal tract in each animal at the time of the experiment produced no growth, it is doubtful if complete bacterial sterilization was attained.

The contribution of ammonia formed in the intestinal tract via the breakdown of urea to carbamate and carbamide in the presence of carbonic anhydrase (Fig. 1) was investigated in 3 experiments. Five hundred milligrams of carbonic anhydrase inhibitor (Diamox) was given intravenously 30 minutes before hemorrhage and every hour thereafter during the experiment.

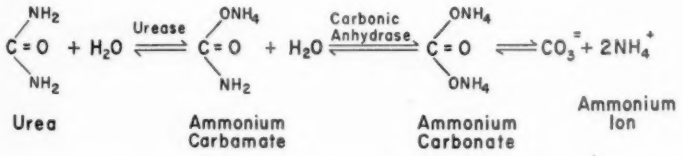


Fig. 1.—Ammonia formation from urea via carbamate and carbamide in presence of carbonic anhydrase.

Because of the reported alteration in response to hemorrhage following the administration of certain adrenolytic agents[42] and bile salt preparations,[20] Dibenzyline (2 mg. per kilogram per minute) and Decholin (2 mg. per kilogram per minute) were given to 4 dogs as a constant intravenous infusion during the entire experiment.

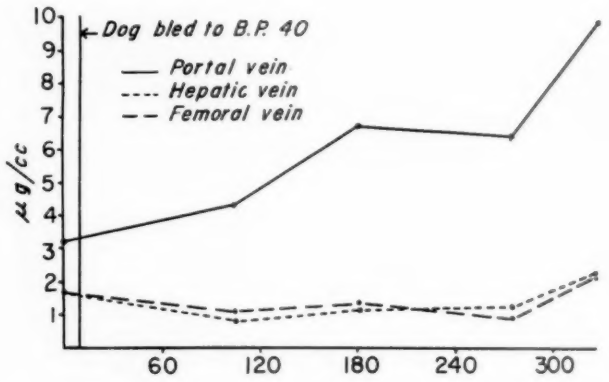


Fig. 2.—Blood ammonia concentrations in hemorrhagic shock.

## RESULTS

A summary of the ammonia concentrations of portal, hepatic, and peripheral venous blood as correlated with blood pressures, amount of blood shed, estimated hepatic blood flow time, and pre-experiment treatment is shown in Tables I and II. Graphic representation of a typical experiment is shown in Fig. 2. From these data it is apparent that the portal blood ammonia concentration rises progressively with hemorrhage and that such elevations are proportional to the degree and time of blood loss. The mean rise in portal ammonia concentration in deep shock (loss of 40 per cent blood volume) was 4.2 mg. per cent, or 245 per cent of normal. It is further apparent that such elevations are reversible with early restoration of normal blood volume and that there is no significant elevation of the ammonia concentrations in either the hepatic or peripheral venous blood until the preterminal phases of shock,

when hypotension of 40 mm. Hg or less had been maintained for 2 to 4 hours. This indicates that even in the presence of profound and long-standing blood loss and hepatic anoxia there is sufficient hepatic reserve for normal conversion of portal blood ammonia. Only in far-advanced shock is this reserve consumed, when the liver fails to clear the portal blood of its ammonia load and the hepatic and peripheral vein ammonia concentrations are elevated. This is essentially limited to agonal event.

A summary of the findings during hemorrhagic shock in the 3 dogs receiving oral antibiotics is shown in Table III. One of these experiments is

TABLE I. BLOOD AMMONIA CONCENTRATION IN HEMORRHAGIC SHOCK (WIGGERS TECHNIQUE)

| DOG NO. | MINUTES FOLLOWING INITIAL HEMORRHAGE | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Time | 0 | 1 | 90 | 154 | 188 | 250 | 310 | | |
| 16.6 Kg. | % Bl. loss | | 47 | 47 | 62 | 8 | 8 | 11 | | |
| Bl. vol. | Blood press. | 120 | 50 | 20 | 50 | 140 | 110 | 110 | | |
| 1640 ml. | E.H.B.F. | 320 | | 290 | 212 | | 765 | 1640 | | |
| Unanesthetized | Periph. $NH_3$ | 2.8 | | | 4.4 | | 5.3 | | | |
| | Hepatic $NH_3$ | 2.0 | | | 0.9 | | 2.6 | | | |
| | Femoral $NH_3$ | 1.5 | | | 1.6 | | 1.9 | | | |
| 2 | Time | 0 | 32 | 95 | 133 | 310 | | | | |
| 19 Kg. | % Bl. loss | | 33 | 40 | 43 | 38 | | | | |
| Bl. vol. | Blood press. | 150 | 75 | 70 | 45 | 50 | | | | |
| 2100 ml. | E.H.B.F. | 760 | 535 | 335 | 215 | 190 | | | | |
| Anesthetized | Periph. $NH_3$ | 2.9 | 6.7 | | 5.6 | 9.0 | | | | |
| | Hepatic $NH_3$ | 1.5 | 0.9 | | 1.6 | | | | | |
| | Femoral $NH_3$ | 1.3 | | | 2.0 | 2.3 | | | | |
| 3 | Time | 0 | 88 | 135 | 265 | | | | | |
| 17.2 Kg. | % Bl. loss | | 36 | 38 | 19 | | | | | |
| Bl. vol. | Blood press. | 145 | 50 | 50 | 30 | | | | | |
| 1530 ml. | E.H.B.F. | 305 | 215 | 250 | 175 | | | | | |
| Anesthetized | Periph. $NH_3$ | 2.7 | | 3.4 | 6.1 | | | | | |
| | Hepatic $NH_3$ | 1.9 | | 2.2 | 3.9 | | | | | |
| | Femoral $NH_3$ | | | | | | | | | |
| 4 | Time | 0 | 40 | 73 | 125 | 215 | 280 | 332 | | |
| 22 Kg. | % Bl. loss | | 38 | 38 | 43 | 10 | 13 | 15 | | |
| Bl. vol. | Blood press. | 150 | 70 | 65 | 40 | 105 | 105 | 115 | | |
| 1755 ml. | E.H.B.F. | 370 | 150 | 90 | 195 | 1100 | 455 | 800 | | |
| Anesthetized | Periph. $NH_3$ | 1.6 | | 1.8 | 8.3 | 3.1 | 4.3 | | | |
| | Hepatic $NH_3$ | 1.1 | | .75 | 8.5 | 1.8 | 0.9 | | | |
| | Femoral $NH_3$ | 1.1 | | 2.2 | 3.2 | 1.8 | 1.4 | | | |
| 5 | Time | 0 | 1 | 26 | 80 | 130 | 212 | 275 | 341 | |
| 17.3 Kg. | % Bl. loss | | 30 | 30 | 33 | 38 | 11 | 13 | 15 | |
| Bl. vol. | Blood press. | 140 | 60 | 70 | 65 | 30 | 90 | 100 | 105 | |
| 1650 ml. | E.H.B.F. | 350 | | 160 | 135 | 65 | 870 | 285 | 1090 | |
| Anesthetized | Periph. $NH_3$ | 4.4 | | | 6.5 | 9.8 | 5.0 | 4.6 | | |
| | Hepatic $NH_3$ | 1.1 | | | 0.1 | 6.0 | 1.1 | 1.3 | | |
| | Femoral $NH_3$ | 1.6 | | | 1.6 | 1.5 | 1.8 | 1.8 | | |
| 6 | Time | 0 | 2 | 16 | 97 | 149 | 235 | 292 | 377 | 442 |
| 12.5 Kg. | % Bl. loss | | 25 | 25 | 27 | 34 | 16 | 20 | 22 | 22 |
| Bl. vol. | Blood press. | 155 | 50 | 65 | 80 | 45 | 115 | 110 | 75 | 30 |
| 1260 ml. | E.H.B.F. | 1210 | | 435 | 380 | 135 | 2520 | 860 | | |
| Anesthetized | Periph. $NH_3$ | 2.9 | | | 2.4 | 6.1 | 3.9 | 6.9 | 8.3 | 9.3 |
| | Hepatic $NH_3$ | 1.8 | | | 1.6 | 2.4 | 2.0 | 2.0 | 1.5 | 3.8 |
| | Femoral $NH_3$ | 1.6 | | | 1.4 | 1.6 | 2.3 | 2.0 | 1.5 | 0.9 |

E.H.B.F. = estimated hepatic blood flow ml./min.
Ammonia concentrations in μg./ml.
Heavy vertical line is time blood reinfused.

TABLE II. BLOOD AMMONIA CONCENTRATION IN GRADUATED HEMORRHAGE

| DOG NO. | MINUTES FOLLOWING INITIAL HEMORRHAGE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 7 | Time | 0 | 8 | 68 | 176 | 228 | | | |
| 13.4 Kg. | % Bl. loss | | 38 | 44 | 42 | 38 | | | |
| Bl. vol. | Blood press. | 145 | 50 | 35 | 35 | 30 | | | |
| 1435 ml. | E.H.B.F. | 631 | 267 | 153 | 238 | 171 | | | |
| | Portal $NH_3$ | 3.1 | 4.3 | 6.7 | 6.4 | 8.6 | | | |
| | Hepatic $NH_3$ | 1.8 | 0.7 | 1.1 | 1.1 | 2.2 | | | |
| | Periph. $NH_3$ | 1.8 | 1.1 | 1.4 | 0.8 | 2.1 | | | |
| 8 | Time | 0 | 6 | 65 | 107 | 142 | | | |
| 12.5 Kg. | % Bl. loss | | 28 | 36 | 43 | 45 | | | |
| Bl. vol. | Blood press. | 140 | 40 | 40 | 20 | 0 | | | |
| 1210 ml. | E.H.B.F. | 800 | 382 | 393 | 190 | 0 | | | |
| | Portal $NH_3$ | 3.97 | | 6.3 | 5.6 | | | | |
| | Hepatic $NH_3$ | 1.28 | | 1.23 | 1.1 | | | | |
| | Periph. $NH_3$ | 1.43 | | | 2.7 | | | | |
| 9 | Time | 0 | 90 | | | | | | |
| 18 Kg. | % Bl. loss | | 32 | | | | | | |
| Bl. vol. | Blood press. | 145 | 50 | | | | | | |
| 2170 ml. | E.H.B.F. | 950 | 139 | | | | | | |
| | Portal $NH_3$ | 2.7 | 4.5 | | | | | | |
| | Hepatic $NH_3$ | 1.6 | 1.0 | | | | | | |
| | Femoral $NH_3$ | 1.6 | 1.5 | | | | | | |
| 10 | Time | 0 | 2 | 26 | 67 | 137 | 187 | 207 | 245 |
| 18 Kg. | % Bl. loss | | 16 | 11 | 21 | 36 | 40 | 43 | 46 |
| Bl. vol. | Blood press. | 150 | 140 | 135 | 130 | 75 | 50 | 40 | 20 |
| 2141 ml. | E.H.B.F. | 710 | 483 | 600 | 400 | 255 | 255 | 240 | 220 |
| | Portal $NH_3$ | 2.3 | | 3 | 3.7 | 6.8 | 7 | | |
| | Hepatic $NH_3$ | 1.1 | | 1.3 | 2.2 | 1.2 | 1.7 | | |
| | Femoral $NH_3$ | 1.1 | | 1.1 | 2.0 | | 2.4 | | |
| 11 | Time | 0 | 33 | 98 | 113 | 185 | 213 | | |
| 17.4 Kg. | % Bl. loss | | 15 | 30 | 35 | 50 | 56 | | |
| Bl. vol. | Blood press. | 130 | 110 | 95 | 90 | 50 | 25 | | |
| 1390 ml. | E.H.B.F. | 460 | 340 | 209 | 255 | 144 | 110 | | |
| | Portal $NH_3$ | 2.8 | 3.1 | | 4.0 | 5.4 | | | |
| | Hepatic $NH_3$ | 1.2 | 1.7 | | 1.3 | 1.4 | | | |
| | Femoral $NH_3$ | 1.7 | 1.5 | | 1.9 | | | | |

E.H.B.F. = estimated hepatic blood flow in ml./min.
Ammonia concentrations in μg./ml.
All animals anesthetized.

illustrated in graphic form in Fig. 3 and shows that there is no alteration in the pattern of ammonia blood level response. Ammonia arising from the portal bed does not, therefore, depend in any appreciable degree upon alteration of bacterial action, a fact that might well have been predicted on the immediacy of the response to hemorrhage.

The findings in the 3 dogs receiving carbonic anhydrase inhibitor (Diamox) did not different significantly from the controls, suggesting that portal bed ammonia does not arise from the breakdown of urea to carbamate and carbamide with the enzymatic action of carbonic anhydrase. One such experiment is illustrated in Fig. 4.

Blood ammonia studies of the 4 animals given either Decholin or Dibenzyline showed no significant variation from the control animals.

No appreciable difference in ammonia levels was found between animals in which hepatic and portal venous blood samples were obtained by needle puncture

TABLE III. AMMONIA CONCENTRATIONS IN HEMORRHAGIC SHOCK WITH STERILE INTESTINAL TRACT

| DOG NO. | | MINUTES FOLLOWING INITIAL HEMORRHAGE | | | | | | | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Time | 0 | 2 | 80 | 98 | 144 | 231 | 284 | 336 | Tetracycline 1 |
| 22.7 Kg. | % Bl. loss | | 36 | 36 | 36 | 49 | 10 | 12 | 13 | Gm. daily 4 |
| Bl. vol. | Blood press. | 140 | 45 | 95 | 105 | 45 | 135 | 125 | 150 | times prior to |
| 2280 ml. | E.H.B.F. | 360 | | 275 | 315 | 205 | 725 | 450 | 495 | experiment |
| | Portal $NH_3$ | 2.8 | | | 4.8 | 6.0 | 3.0 | | 3.4 | |
| | Hepatic $NH_3$ | 1.3 | | | 1.3 | 3.0 | 1.7 | | 1.8 | |
| | Femoral $NH_3$ | 1.5 | | | 1.3 | 1.1 | 1.6 | | 1.6 | |
| 2 | Time | 0 | 50 | 92 | 135 | 210 | 275 | | | Tetracycline 2.5 |
| 18.1 Kg. | % Bl. loss | | 35 | 39 | 40 | 15 | 19 | | | Gm. daily 3 |
| Bl. vol. | Blood press. | 150 | 70 | 50 | 35 | 100 | 110 | | | times, 5 Gm. |
| 1430 ml. | E.H.B.F. | 860 | 185 | 109 | 170 | 575 | 510 | | | daily 3 times |
| | Portal $NH_3$ | 2.1 | | 4.8 | 4.6 | 3.7 | 2.1 | | | and 5 Gm. 6 |
| | Hepatic $NH_3$ | 1.5 | | 1.6 | 2.1 | 2.2 | 1.2 | | | hours prior to |
| | Femoral $NH_3$ | 1.6 | | 1.6 | 1.3 | 2.0 | 2.0 | | | experiment |
| 3 | Time | 0 | 51 | 83 | 128 | 198 | 254 | | | Tetracycline 2.5 |
| 14.5 Kg. | % Bl. loss | | 37 | 40 | 49 | 16 | 20 | | | Gm. b.i.d. 6 |
| Bl. vol. | Blood press. | 130 | 65 | 50 | 30 | 130 | 130 | | | times and 5 |
| 1330 ml. | E.H.B.F. | 560 | 205 | 255 | 170 | 480 | 195 | | | Gm. 6 hours |
| | Portal $NH_3$ | 1.6 | | 4.0 | 6.0 | 2.6 | | | | prior to ex- |
| | Hepatic $NH_3$ | 1.0 | | 7.3 | 2.0 | 2.1 | | | | periment |
| | Femoral $NH_3$ | 1.2 | | 1.7 | 1.4 | 1.6 | | | | |

E.H.B.F. = estimated hepatic blood flow in ml./min.
Ammonia concentrations in μg./ml.
Heavy vertical line is time blood reinfused.
All animals anesthetized.

during laparotomy and those in which London cannulae were employed in the unanesthetized dogs.

Correlation of blood flow and ammonia concentration within the portal vein is illustrated in Table IV, and one such experiment is shown in Figs. 5 and 6. It is evident that the ammonia concentration increases proportionate to the diminution in portal blood flow, so that the total ammonia production within

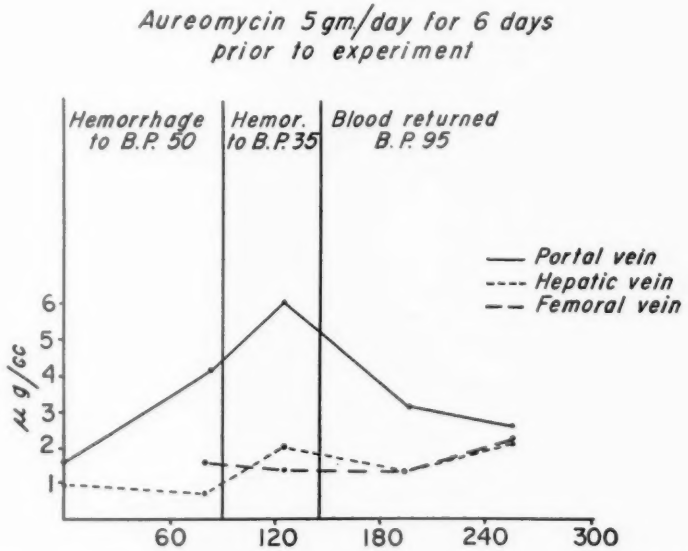


Fig. 3.—Blood ammonia levels in hemorrhagic shock in animal with sterilized intestinal tract.

TABLE IV. BLOOD AMMONIA CONCENTRATIONS AND PORTAL BLOOD FLOW IN HEMORRHAGIC SHOCK

| DOG NO. | | MINUTES FOLLOWING PORTAL VEIN CANNULATION | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 30 | 60 | 90 | 120 | 160 | 180 | 210 | 270 | |
| 1 | B.P. | | | 120 | 90 | 65 | 35 | 30 | | | |
| | Portal flow | | | | 360 | | 125 | | | | |
| | Portal $NH_3$ | | | 2.87 | 3.44 | | | 3.84 | | | |
| | Hepatic $NH_3$ | | | | | .93 | | 1.02 | | | |
| | Periph. $NH_3$ | | | | | .32 | | | .52 | | |
| 2 | B.P. | | 110 | | 60 | 50 | | 45 | 40 | | 20 ml. blood withdrawn at 40 minutes |
| | Portal flow | | 456 | | 300 | 276 | | 228 | 210 | | |
| | Portal $NH_3$ | | 4.29 | | >6.3 | | | 5.41 | >6.3 | | |
| | Hepatic $NH_3$ | | .57 | | .63 | | | .51 | | | |
| | Periph. $NH_3$ | | | | .41 | | | .52 | | | |
| 3 | B.P. | | | 110 | 100 | 70 | | | 50 | | 150 ml. blood withdrawn at 97 minutes |
| | Portal flow | | | | 480 | 308 | | | 294 | | |
| | Portal $NH_3$ | | | 1.61 | | 1.8 | | | 4.4 | | 30 ml. blood withdrawn at 170 minutes |
| | Hepatic $NH_3$ | | | .48 | | .55 | | | | | |
| | Periph. $NH_3$ | | | | | .52 | | | | | |
| 4 | B.P. | 160 | | 105 | 95 | | 40 | | 20 | | Bleeding from portal cannula at 10 minutes |
| | Portal flow | | | 396 | 378 | | 240 | | 144 | | |
| | Portal $NH_3$ | 1.99 | | | 2.39 | | 3.78 | | >4.14 | | 60 ml. blood withdrawn at 95 minutes |
| | Hepatic $NH_3$ | .45 | | | .45 | | .09 | | 2.53 | | |
| | Periph. $NH_3$ | .74 | | | .39 | .49 | .84 | | | | |
| 5 | B.P. | | 160 | | | 90 | 80 | 60 | 40 | 20 | |
| | Portal flow | | | | | 510 | 396 | 360 | 204 | 192 | |
| | Portal $NH_3$ | | 2.5 | | | >5.63 | >5.63 | | | >5.63 | |
| | Hepatic $NH_3$ | | 1.0 | | | .79 | .83 | | | 2.2 | |
| | Periph. $NH_3$ | | | .63 | | | .87 | | | .44 | |
| 6 | B.P. | 150 | | 140 | 100 | 60 | 40 | 20 | 10 | 10 | |
| | Portal flow | | | 540 | 468 | 210 | 186 | | 42 | 30 | |
| | Portal $NH_3$ | | | 1.72 | 6.72 | | 8.0 | | 15+ | | |
| | Hepatic $NH_3$ | | | .83 | | .50 | | 3.54 | | 4.83 | |
| | Periph. $NH_3$ | | | .92 | | .53 | .18 | | | 1.04 | |

B.P. = systolic blood pressure.
Portal flow = ml./min.
Ammonia concentrations in μg./ml.

the portal bed is unaltered following hemorrhage and the ammonia load is no greater than normal. Should the shed blood be retained within the intestinal tract, these conditions obviously do not apply.

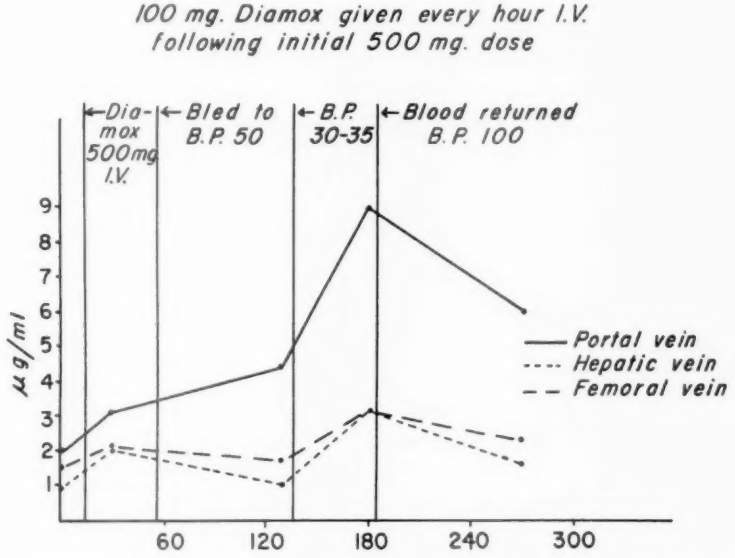


Fig. 4.—Blood ammonia levels in hemorrhagic shock in animal treated with carbonic anhydrase inhibitor.

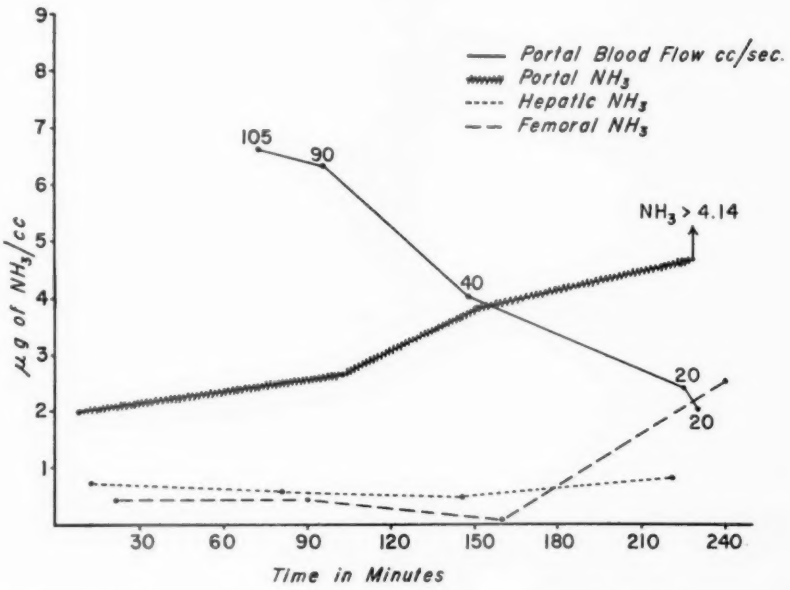


Fig. 5.—Blood ammonia concentrations and portal blood flow in typical animal in hemorrhagic shock.

## DISCUSSION

Increase in portal blood ammonia concentration during hemorrhage is in agreement with previous reports,[29] but correlation with simultaneous blood flow measurements indicates no significant alteration in production of ammonia

within the portal bed. More exact measurement of blood flow in the intact vein might show a minor alteration in ammonia production within the portal bed as occurs in the peripheral tissues following hemorrhage.[44]

These data do not indicate any abnormal production of portal ammonia during hemorrhagic shock except to exclude the primary role of bacterial action and carbonic anhydrase in its production; previously it has been suggested that most of the ammonia arises from bacterial action.[15]

There is sufficient hepatic reserve for the conversion of portal blood ammonia to maintain normal peripheral blood ammonia concentrations in all but the most advanced stages of shock, just as this function has been found to be unimpaired following massive resections of the liver.[22]

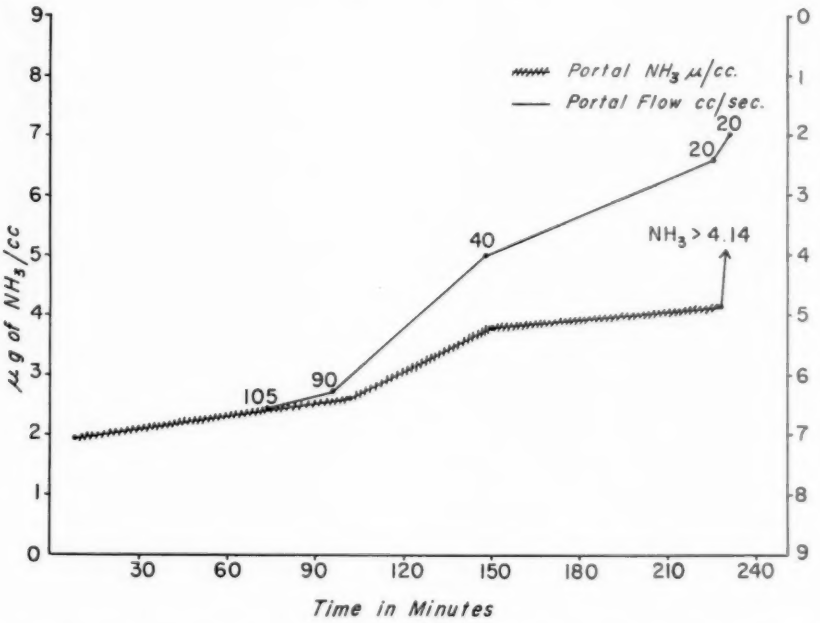


Fig. 6.—Blood ammonia concentrations and portal blood flow in one animal in hemorrhagic shock with blood flow plotted reciprocally to emphasize diminution of blood flow paralleling increasing portal blood ammonia concentrations.

These experiments suggest that alteration in ammonia metabolism in response to blood loss is not of primary importance either in the pathogenesis of shock or in the hepatic coma and ammonia intoxication resulting from bleeding esophageal varices. Ammonia intoxication in the latter condition can better be explained by the breakdown and absorption of blood within the intestinal tract.

## SUMMARY

1. During experimental hemorrhagic shock there is an increase in the ammonia concentration of portal venous blood which is dependent neither on bacterial action nor on carbonic anhydrase activity.

2. Correlation of portal venous blood flow and ammonia concentration indicates no increase in portal ammonia production following hemorrhage.

3. An increase in peripheral blood ammonia concentration indicating hepatic failure in ammonia conversion occurs only in the most advanced stages of shock.

4. The significance of these findings is discussed in relation both to the pathogenesis of shock and to hepatic coma and ammonia intoxication resulting from bleeding esophageal varices.

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# AN EXPERIMENTAL STUDY OF FAT EMBOLISM

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## INTRODUCTION

NUMEROUS thorough studies have been made of clinical and pathologic changes occurring in fat embolism. The concomitant physiologic alterations, however, have not received comparable attention. Many experiments were made using supposedly bland substances other than fat. The applicability of these to the problem is only partial, however.

In 1920, Dunn[3] attempted to obstruct pulmonary vessels mechanically by introducing an emulsion of potato starch in saline (1 to 4) into the jugular vein or right ventricle. Immediately following injection, the respiratory rate decreased for 1 to 7 minutes; then it quickened and gradually rose to a level higher than normal. Large doses led to death in 5 to 30 minutes; moderate doses, in 1¼ to 8 hours. Respirations ceased before the heartbeat. Dyspnea was noted without arterial or venous oxygen desaturation. No constant relation between dyspnea and alterations in cardiac output was observed. There was arterial hypotension and a high venous pressure.

Harman and Ragaz,[5] in 1950, injecting the alcoholic extract of homologous fat into rabbits, reported that the mortality rate varied with dosage but not with changes in the rate of injection.

Embolization of the lungs by the fat produced acute vascular and parenchymal changes which did not occur in any of the other organs. No such pulmonary lesions could be demonstrated after embolization with paraffin. Considering the irritative nature of long chain fatty acids on the tissues of the lung[6] and the presence of lipase in the alveolar septa,[4] it was felt that the lesions were the results of hydrolysis of the embolized fat in the lung and inflammation produced by the released fatty acids.

Price, Hata, and Smith,[10] in 1955, studied the effects of multiple small emboli and the dynamics of the resulting pulmonary hypertension. Barium sulfate suspension was the source of emboli. Despite injection into lobar arteries, the barium always was found quite uniformly distributed throughout the lungs. Open chest experiments in dogs showed (1) increased pulmonary artery pressure with decrease in systemic blood pressure, (2) dilatation of the right auricle and ventricle with poor filling of left heart, (3) decrease in cardiac output, and (4) no change in left atrial pressure.

Niden and Aviado,[9] in the past year, reported on pulmonary embolism induced by the injection of glass beads 60 to 420 micra in diameter in dogs.

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Initially, the Jarisch-Bezold reflex, consisting of systemic hypotension, bradycardia, and apnea, was observed. This was succeeded by hyperpnea and partial or complete recovery of blood pressure and pulse rate. After injection, the pulmonary artery pressure rose in proportion to the dosage of glass beads. Direct embolization of proximally occluded lobar pulmonary artery branches shows that reflex generalized spasm of the pulmonary arterial bed may result, mediated through autonomic pathways. The components of pulmonary embolism were concluded to be (1) primary mechanical obstruction, (2) secondary local vasoconstriction, and (3) arterial spasm involving pulmonary arteries in the rest of the lung.

## EXPERIMENTAL METHODS AND PROCEDURES

The study consisted of 3 connected parts, using homologous fat that had been minimally altered. Acute experiments were performed to evaluate the effects of fat embolism on cardiovascular dynamics and respiration. Because of the clinical occurrence of peripheral embolization after pulmonary involvement the role of the pulmonary capillary bed in the passage of fat emboli was investigated. Finally, because of suggested inflammatory lesions produced by fat in the lungs, a long-term study was undertaken to evaluate the late hemodynamic and histologic effects of fat embolism.

*Preparation of Injected Fat.*—Omental and perinephric fat was removed from freshly killed dogs. It was macerated for 15 minutes in a Waring blender and filtered through multiple layers of gauze. The filtrate was then heated to 45° C. and centrifuged. Fat was obtained as a clear, faintly yellow supernatant. This had a melting point between 34° and 36° C., by the capillary tube method.

*Preparation of Animals.*—Mongrel dogs weighing between 8.2 and 30 Kg. were used in these experiments. They were anesthetized with 30 mg. per kilogram sodium pentobarbital administered intravenously. Using aseptic technique, thoracotomy was performed in the left fourth intercostal space. Endotracheal oxygen was administered using intermittent positive pressure.

*Needle guides:* These were made of polyethylene and were sutured to the main pulmonary artery and the left auricle intrapericardially.[7] They were brought out through the third and fifth intercostal spaces, respectively, with the open ends fixed in the subcutaneous tissues.

*Snares:* In some animals the 2 branches of the pulmonary artery to the left lower lobe were dissected out and each was surrounded by a polyethylene snare, the ends of which were fixed subcutaneously. When drawn tight, these snares occluded arterial inflow, and thus protected the lobe from embolization.

*Fat Injection and Recording.*—The dogs were anesthetized with the least necessary dose of sodium pentobarbital to permit the relatively painless manipulations. All retained swallowing and lid reflexes with a dose averaging 25 mg. per kilogram. No. 18 spinal needles were inserted into the vessels through the needle guides. The femoral artery was cannulated, and a polyethylene tube was inserted into the pleural cavity. In some dogs, a catheter was placed in the right atrium. Respiratory patterns could be analyzed from

either of the latter 2 tracings. All these were attached to previously standardized strain gages connected to a Hathaway pressure recording apparatus, with a photographic oscillograph. The fat was warmed to 37° C. and injected with 5 c.c. of isotonic citrate through a polyethylene cannula into the jugular vein or through a No. 15 needle into the lingual vein, as rapidly as was possible (in 2 to 10 seconds).

Dogs prepared with snares had these tightened prior to the injection, occluding the pulmonary arteries to segments of the left lower lobe and, thus, protecting these from embolization. They were released after given periods of occlusion. Recordings were taken prior to injection, through the time of snare-occlusion and continuously during and after the injection of fat. They were continued either until the dog died or, in survivors, until the pressures had stabilized.

The photographic records were analyzed using planigraphy to obtain mean pressures in addition to the more obvious recorded data. Post-mortem studies were done immediately after the acute deaths. The survivors were autopsied 1 and 3 months after injection. Histologic studies included examination of the lung, brains, kidneys, liver, spleen, and pancreas. Fat stains were prepared on frozen sections using Sudan III. Formalin fixed tissues were stained routinely with hematoxylin and eosin.

*Fat Sampling Studies.*—In order to evaluate the capacity of the lungs to filter out fat simultaneous samples of blood from the pulmonary artery and the left auricle were withdrawn during and after the injection of fat. This was done in several fashions. Needles were inserted into the vessels through needle guides. At first, samples were taken using 2 c.c. syringes as fast as was possible immediately following injection. In the second method, continuous samples were withdrawn over a 30-second interval beginning at the time of injection into 8-foot-long siliconized polyethylene tubes. The tubes were then subdivided by clamping into segments containing 2 c.c. of blood, and these aliquots were removed for analysis. Finally, Becton-Dickinson automatic pipetting outfits were used. These are automatically filling syringes which permit withdrawal through one opening and ejection through another. Two cubic centimeter samples from the pulmonary artery and left auricle were taken in a rapid sequence and collected in separate test tubes. Total serum lipids were determined by the turbidimetric method of de la Huerga, Yesinick, and Popper,[8] using the preinjection serum as the blank.

## RESULTS

### Acute Study.—

*Mortality.*—Twenty-seven dogs injected with varying amounts of fat out of a total of 32 in the present study can be used to evaluate the mortality resulting from various doses. The other 5 dogs were bled for fat filtration experiments and, therefore, are not included here. Table I outlines the results. The $LD_{50}$, as determined in a probit analysis by the graphic method, was 1.38 c.c. per kilogram. Two cubic centimeters per kilogram invariably proved fatal.*

*We are indebted to Dr. Colin White of the Department of Public Health for advice and help in the statistical analysis.

*Clinical Study.*—The clinical response of dogs to the injection of fat was quite uniform, with changes varying in extent depending on dosage. During the injection and immediately after, the animals became apneic and the pulse slowed. Cyanosis soon appeared, and when spontaneous respirations reappeared they were deep, slow, and often in a Cheyne-Stokes pattern, utilizing primary as well as accessory muscles of breathing. Occasionally, however, particularly in dogs which later died, there was a brief period of extreme tachypnea produced by the intercostal muscles without signs of diaphragmatic action.

TABLE I

| DOSAGE OF FAT (C.C./KG.) | NUMBER OF DOGS | DIED | SURVIVED |
|---|---|---|---|
| 0.33 | 4 | 1 | 3 |
| 0.50 | 4 | 1 | 3 |
| 0.75 | 2 | 0 | 2 |
| 1.00 | 3 | 1 | 2 |
| 1.33 | 1 | 1 | 0 |
| 1.50 | 4 | 2 | 2 |
| 2.00 | 9 | 9 | 0 |
| | 27 | 15 | 12 |

All dogs improved clinically after the immediate effects had worn off, in 2 to 3 minutes. Color became better, heart rate speeded up, and respirations became more regular. This improvement persisted and continued in the animals that were to survive. Dogs having received the larger dosages, however, did not maintain this status. They had tachycardia, respirations became shallow and irregular again, and the animals ultimately died cyanotic with respiratory arrest, extreme tachycardia, and probably ventricular fibrillation. All deaths occurred within one hour after the injection of fat, usually between 4 and 15 minutes.

The survivors improved steadily with stabilizing vital signs. X-ray studies of the chest in 3 dogs 1 hour and 36 hours after injection showed no changes from the preinjection films. On recovering from the anesthetic and throughout the ensuing 3 months (after which they all were sacrificed), there were no sequelae of any sort evident. Neurologic examinations showed no defects, behavior was not obviously altered, and all dogs gained or maintained their weight.

*Physiologic Study.*—A typical physiologic pattern of response was obtained in all animals. This correlated well with the clinical picture. Even during injection the pressure in the pulmonary artery rose, and within seconds the peripheral arterial pressure and heart rate dropped. In 2 dogs receiving fat in a dosage of 2 c.c. per kilogram, right auricular pressures were also recorded. This rose in both cases peaking at 37 and 41 seconds after injection, respectively, at 17.2 and 16.3 cm. water above preinjection levels. Apnea of varying lengths was present in all but one animal. Gradually, the pulmonary and femoral artery pressures began to return to normal; maximal changes occurred 15 seconds after the beginning of the injection (that is, 5 to 13 seconds after its termination). Surviving animals showed a steady return to normal pressures and rates. Animals that were to die showed incomplete return of peripheral arterial pressures to normal. Improvement persisted, however, only until

the pulmonary artery pressures had returned to normal. After this had occurred (usually in a period of 3 to 7 minutes), there was onset of tachycardia, with gradual diminution in femoral artery pressure, respiratory irregularity, and, ultimately, death. Segments of a typical tracing are shown in Fig. 1.

The above changes are recorded quantitatively in Table II. There is no correlation between the magnitude of pressure changes and ultimate survival or death. Neither did the rate of return of systemic arterial pressures toward normal seem to be of prognostic importance.

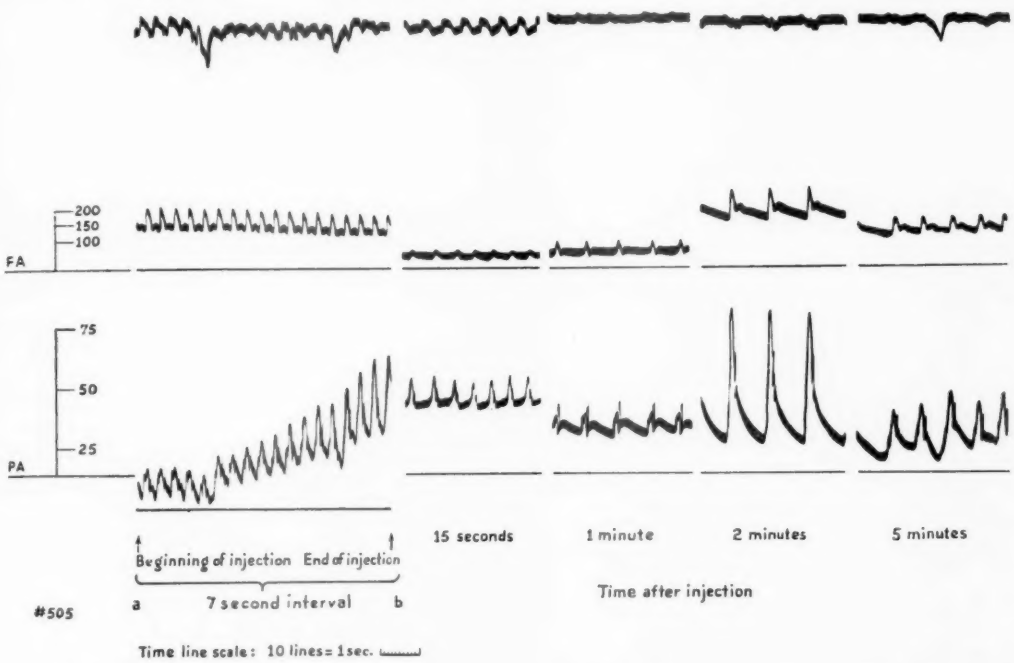


Fig. 1.—Dog 505 (see Table II). Segments of pressure recording (retouched for photographic contrast) showing the effects of the injection of 1.50 c.c. per kilogram of fat. The top tracing is of intrapleural pressure; small deflections are produced by cardiac action, large ones by respiration. The middle tracing is of femoral artery (FA) pressure; the lowest is of main pulmonary artery (PA). Early rise of PA pressure is shown during injection, with a slight downward trend in the FA. There are apnea, bradycardia, systemic hypotension, and persistent pulmonary hypertension at 15 seconds. Gradual re-establishment of PA and FA pressures occurs over the next 5 minutes, and respirations return.

*Pathologic Study.—*

*Gross:* All dogs were deeply cyanotic. On opening the chest, the lungs collapsed easily and showed some gross evidence of congestion. The heart was uniformly dilated, particularly on the right side. Free fat globules were found in the blood from both sides of the heart.

*Microscopic:* Eight animals were studied. Frozen sections of the lungs showed large masses of intravascular fat in the pulmonary arteries, and occasionally also in the veins. Lobes protected by snares on the pulmonary artery for 5 to 10 minutes after injection do not contain any fat. Fat was found in the vessels of most peripheral organs studied, including the brain. Hematoxylin and eosin sections showed no lesions.

*Fat Sampling.*—Attempts at measuring the role of the pulmonary bed in filtering out fat were never fully satisfactory, and the results were not reliable.

Continuous withdrawal or rapid intermittent sampling of blood from the pulmonary artery and the left auricle were equally unsatisfactory. No reproducible curve could be established correlating fat content to time elapsed after the injection of the fat. Some samples contained large amounts, while others, drawn just before or after, contained none. The only constant finding was the total absence of fat in blood from the left auricle until immediately prior to death. At all post mortems, on the other hand, the left auricle always contained many grossly visible fat globules.

TABLE II

| DOG NUMBER AND DOSE | LENGTH OF SURVIVAL | LENGTH OF APNEA | MAXIMUM PULMONARY HYPERTENSION* | FEMORAL ARTERY PRESSURE CHANGES* | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | IMMEDIATELY AFTER INJECTION | 1 MIN. | 2 MIN. | 5 MIN. | 10 MIN. |
| 1 c.c./Kg. | | | | | | | | |
| 486 | 4′30″ | 37″ | 30 | − 91 | −131 | −140 | D | |
| 490 | 3 mo. | 55″ | 23 | − 76 | | − 42 | | − 10 |
| 492 | 3 mo. | 1′10″ | 39 | + 5 | − 22 | | − 3 | − 2 |
| 1.33 c.c./Kg. | | | | | | | | |
| 493 | 16′ | 40″ | 39 | − 75 | − 38 | − 6 | + 6 | + 3 |
| 1.50 c.c./Kg. | | | | | | | | |
| 500 | 3 mo. | 2′ | 49 | −176 | − 40 | − 14 | − 14 | − 4 |
| 504 | 4′30″ | Hyperpnea | 28 | − 41 | −103 | −134 | D | |
| 505 | 3 mo. | 13″ | 25 | −134 | −110 | −146 | −104 | − 40 |
| 2.00 c.c./Kg. | | | | | | | | |
| 494 | 7′ | 30″ | 29 | − 87 | − 79 | − 75 | −157 | D |
| 509 | 22′ | 1′15″ | 48 | − 29 | | − 32 | − 32 | − 84 |
| 523 | 8′ | 35″ | 31 | − 37 | − 80 | − 64 | − 86 | D |
| 524 | 26′ | 25″ | 29 | − 22 | − 65 | −139 | −112 | −137 |

*All pressures in mm. Hg. Both the pulmonary and the femoral artery pressure changes are recorded as the differences from the preinjection mean pressures.

LONG-TERM STUDY.—

Physiologic studies were performed in 4 dogs which survived the injection of fat. Two animals were evaluated after 4 weeks and 2 after 3 months, one in each group having received 0.75 c.c. per kilogram of fat, the other 1.00 c.c. per kilogram.

Pressures in both the pulmonary artery and in the left auricle were within the preinjection range in all these dogs.

Histologic studies then were done on these same animals as well as on 2 others that had received 0.50 c.c. per kilogram of fat 3 months previously. Fat stains showed no residual fat in either the lungs or in other parenchymatous organs. The hematoxylin and eosin stained sections showed no abnormalities in either the lungs or in the other organs. The lobes protected by snares revealed no changes which might be attributed to the presence of snares.

## DISCUSSION

Practically all previous experimental studies of fat embolism have been performed using chemically extracted or fractionated fat, thus altered in some fashion, or such nonphysiologic substances as olive oil or paraffin. Therefore, it was felt important to try to reproduce one of the presumed mechanisms in which

this condition arises in man. Fat was prepared without the use of excessive temperatures or chemical solvents so as to alter it minimally or not at all. Marrow embolism was not studied.

The inability to develop a satisfactory sampling method for blood fat is quite puzzling. The explanation probably hinges on physical factors within the vessels tapped. A 2-phase (that is, blood-fat) system, particularly when in nonturbulent flow, will develop a certain layering of components along the vessel wall, depending on their density. Turbulence does disturb this to some extent, but extreme turbulence would be required to produce any degree of homogeneity. It was probably this streaming which made our results vary so greatly; the concentrations depend on which layer the needle happened to tap at the time the sample was withdrawn.

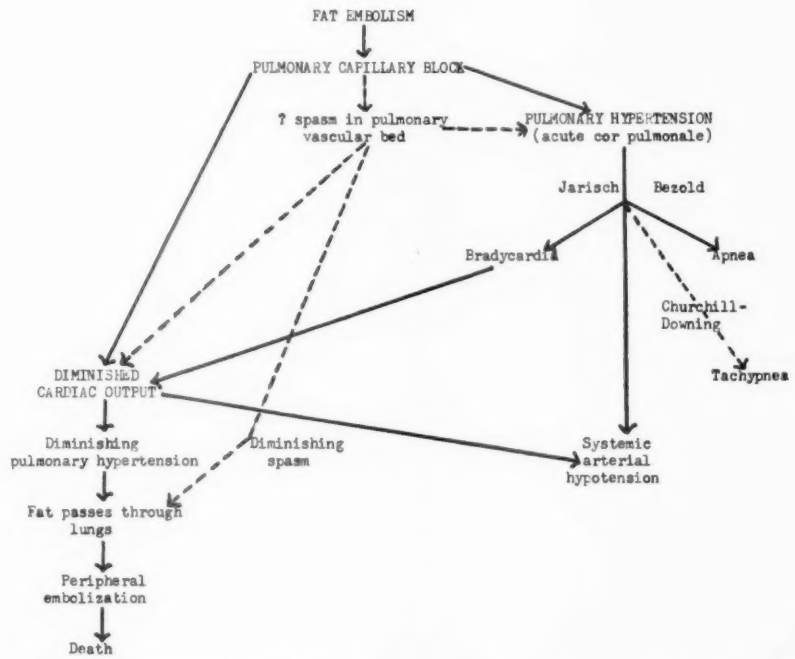


Fig. 2.—Schema indicating possible consequences of fat embolism. One effect of sudden pulmonary hypertension is shown alternatively as apnea (Jarisch-Bezold) or as the rapid shallow breathing described by Churchill and Cope[1] and by Downing.[2]

The one reproducible finding—the inability to find fat on the venous side of the pulmonary circuit until very shortly before death—is of interest, however. It has been described how the initial pulmonary hypertension gradually vanished with some return of systemic pressures toward normal prior to death. Fat was found in the left auricle only after this change had taken place. One wonders if the acute pulmonary hypertension, induced by the embolism, might not actually have served as a protective mechanism (vessels in spasm or blocked would keep fat from passing through capillary beds otherwise permeable). Niden and Aviado[9] have shown local and segmental spasm to occur with bland emboli, and a similar mechanism may be operating here.

The pulmonary hypertension may be caused by one or both of these mechanisms. Hypoxia has been suggested as another possible cause by Price, Hata, and Smith.[10] However, the immediacy of the response argues strongly against this, particularly in the early phase. The physical obstruction of a capillary bed per se will tend to produce an elevation of pressure. This also occurs rapidly. There may be the added factor of spasm in the pulmonary arterial bed, produced by local and/or central reflexes.

The resulting pulmonary hypertension may lead to the other cardiovascular and respiratory changes described. This is the Jarisch-Bezold reflex, consisting of systemic hypotension, bradycardia, and apnea. The peripheral arterial pressure drop is abetted by the diminished cardiac output. The secondary tachypnea is that described by Churchill[1] and by Downing[2] and is the result of distention of the pulmonary vessels. The hypothetical sequence of events is diagrammatically shown in Fig. 2.

The mechanism of death can still not be stated with absolute certainty. Anoxia probably is a significant factor. Niden and Aviado[9] have shown that, in the case of bland emboli, artificial respiration using 100 per cent oxygen will relieve the anoxemia but not prevent death. In this series, however, no attempt was made to overcome respiratory arrest, and this always preceded cardiac standstill. Having shown that embolization of the greater circulation occurs terminally in all animals, the question arises as to whether this is incidental to agonal collapse of the circulation or whether it is the cause of the latter.

It would seem that, in the process of normal dynamics being re-established in the pulmonary circuit, fat (which thus far was held up in the capillary bed) is permitted to pass through it and out into the greater circulation. This, then, embolizes to the brain, producing respiratory arrest and death. The invariable improvement which follows the acute embolic episode, the late appearance of fat on the left side of the heart, and the timing of events all support this hypothesis.

Work emphasizing the role of pulmonary lipase in the production of inflammatory changes after fat embolism stimulated the long-term study. Histologically, the results unequivocally point to lack of chronic effects, under the circumstances of this study. This may be the result of differences of timing. Harman and Ragaz[5] have found vascular changes in the lungs after the lapse of several hours but have followed the animals only for 30 hours. The present histologic follow-up, covering periods ranging from 1 to 3 months, may not have demonstrated any changes because these were reversible and had cleared by the time of sacrifice. The early x-rays, on the other hand, may not have shown the lesions because of their limited extent. Another factor may be the difference in injected fat. The above study employed an alcoholic extract of body fat, refluxed at 80° to 90° C. This method may have led to alterations that might account for the histologic lesions found.

The total lack of neurologic sequelae and the complete recovery after sublethal doses of fat are both features in sharp contrast with the reaction in

man. For this we have no explanation at present. Similarly, the absence of delayed mortality after fat embolism—another characteristic of the condition in man—must go unexplained.

## SUMMARY AND CONCLUSIONS

The effects of fat embolism were studied in dogs. Using homologous fat 2 c.c. per kilogram was uniformly fatal, and the $LD_{50}$ was 1.38 c.c. per kilogram. Intravenous injection of fat produced acute pulmonary hypertension, with apnea, arterial hypotension, and bradycardia (Jarisch-Bezold reflex). Fat was recovered from the left atrium only after return of pulmonary artery pressures toward normal and its appearance was soon followed by death. A temporary protective function by the lung is postulated through the mechanism of holding up fat in its vascular bed (perhaps aided by spasm of the vessels) and thus preventing immediate massive peripheral embolization.

Long-term studies have failed to show demonstrable irreversible changes in the circulation or anatomy of the lung after sublethal fat embolism.

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# SURGICAL REPAIR OF RUPTURED INTERVENTRICULAR SEPTUM FOLLOWING ACUTE MYOCARDIAL INFARCTION

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RUPTURE of the interventricular septum resulting from myocardial infarction is widely recognized as a fatal complication of acute coronary occlusion. In a recent collective review of 132 reported cases of acquired septal rupture, Sanders, Kerr, and Blount[7] stated that 50 per cent died within the first week and that only 13 per cent survived more than 2 months. Schlappi[8] described a rare exception in a surviving case followed 6½ years with findings typical of acquired septal perforation, and 2 other reported cases lived almost 5 years.[9, 10] Actually, the incidence of septal perforation must be significantly greater than reports indicate, not only because the clinical diagnosis was not made before death, but also because perforations are often hidden beneath post-mortem blood clots or the trabeculae carneae, and if the septum is not thoroughly washed at autopsy, a tear can be easily overlooked. Indeed it has been estimated that septal rupture accounts for 1 or 2 per cent of deaths following myocardial infarction.[3]

Septal rupture generally occurs from 4 to 12 days following acute infarction with an average interval of approximately 7 days.[3, 4] Of diagnostic significance in such cases is the sudden appearance of a loud precordial systolic murmur appearing after a coronary occlusion. Death is usually due to rapidly progressive cardiac decompensation. Ante-mortem diagnosis has been made rather consistently in recent years indicating that the complication can be recognized and differentiated clinically from ruptured papillary muscle, fibrinous pericarditis with friction rub, mitral insufficiency secondary to left ventricular dilatation, and other rarer conditions.[1, 4] In only one reported case has cardiac catheterization been done, but this failed to confirm the diagnosis.[7] Since medical therapy is relatively ineffective and futile, prolonging life for only a short period, the stimulus for making a precise diagnosis of acquired perforation of the interventricular septum has been lacking. Recent developments in cardiac surgery, however, have emphasized the need for accurate diagnosis in many other conditions previously considered to be hopeless. Moreover, the development of a mechanical heart-lung apparatus for temporary cardiac bypass has led to the successful correction of congenital defects of the ventricular septum and consequently should provide a means of repairing other complicated cardiac anomalies.[5, 6]

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This report is concerned with a case of acquired perforation of the interventricular septum in which the clinical diagnosis was confirmed by cardiac catheterization, and surgical repair using temporary extracorporeal circulation was performed.

## CASE REPORT

B. S., a 49-year-old white man, was admitted to Methodist Hospital, on March 30, 1956, with intermittent precordial pain, dyspnea, and palpitation. Twelve weeks prior to this admission he first experienced the pain, which radiated into both arms, and had several minor attacks during the ensuing 2 weeks. On Jan. 24, 1956, he was admitted to St. Joseph's Hospital following a sudden more severe attack, and a diagnosis of posteroseptal infarction with right bundle branch block was made from the electrocardiogram (Fig. 1).

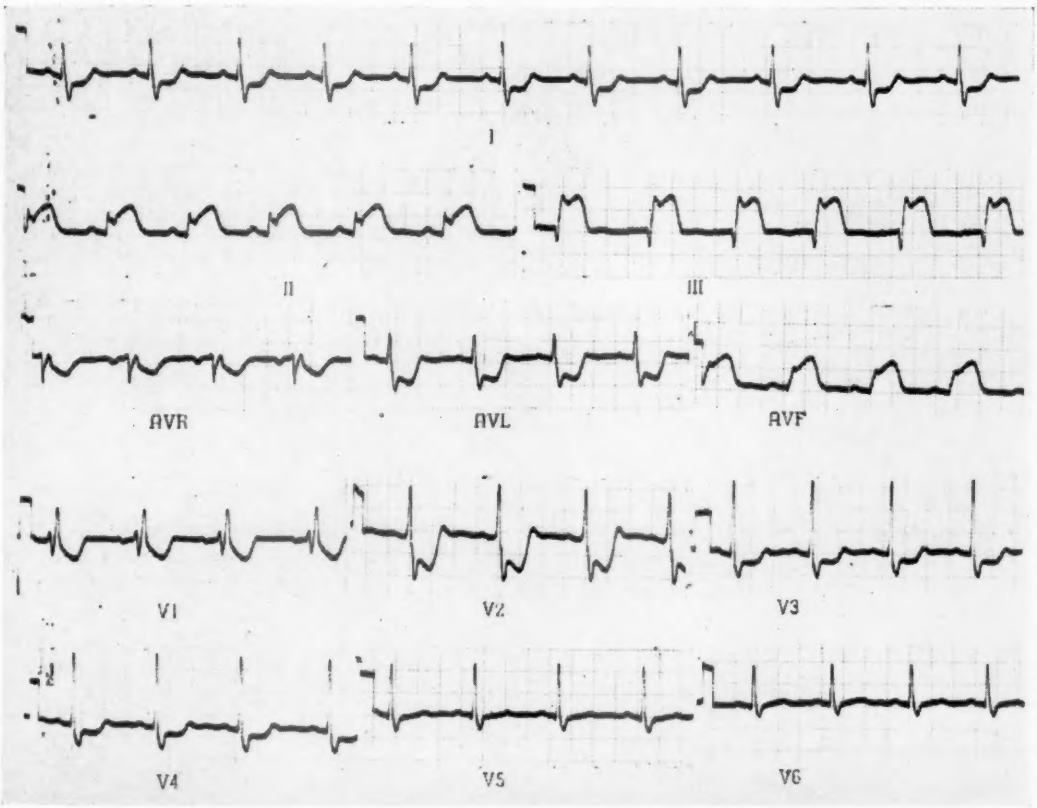


Fig. 1.—Electrocardiogram made at time of initial admission showing acute posteroseptal myocardial infarction with right bundle branch block.

Five days after that admission he had another episode of sudden severe precordial pain and became dyspneic, orthopneic, and cyanotic. Blood pressure, which had previously been approximately 140/90 mm. Hg, was recorded as 90/70 and remained at this level until the present hospitalization. A harsh, precordial systolic murmur was heard along the left sternal border in the fourth intercostal space. It was noted that although the lungs were clear, the liver was enlarged and tender. Following the use of sedatives, oxygen, digitalis, and mercurial diuretics, the acute distress subsided, but he remained in mild failure for several weeks recovering only partially from decompensation. He was discharged following 6 weeks of hospitalization. In spite of a rigid cardiac regimen, he gradually regressed into right and left heart failure.

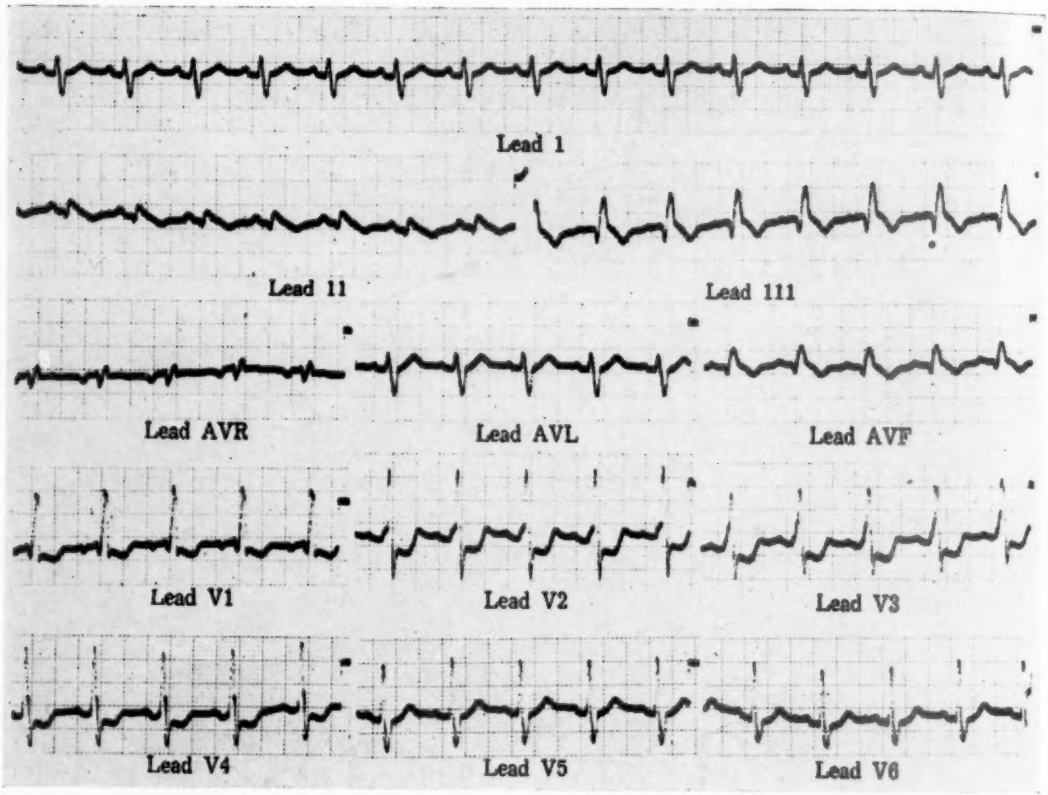


Fig. 2.—Electrocardiogram made 11 weeks later showing evolutionary changes of acute posteroseptal infarction, slight shift of electrical axis to right, right bundle branch block with right auricular and ventricular hypertrophy.

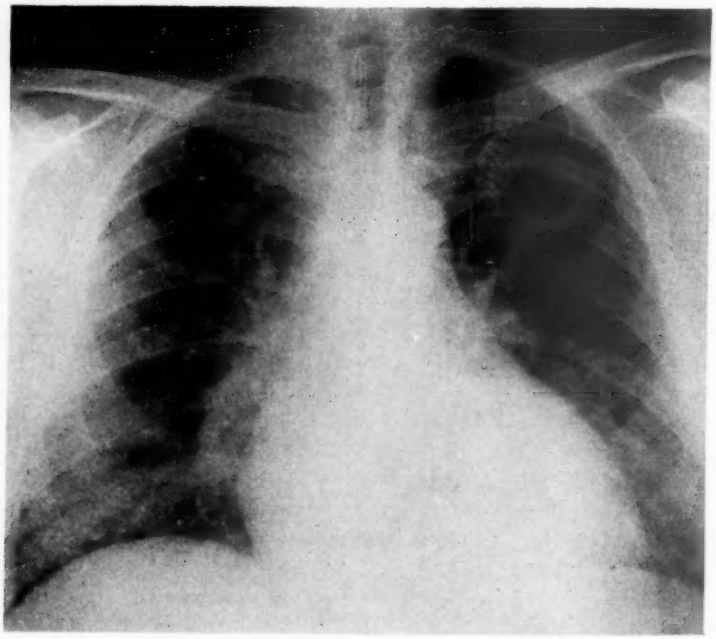

Fig. 3.—Roentgenogram of chest made before operation showing moderate cardiac enlargement and pulmonary congestion.

On this admission physical examination revealed mild distention of neck veins and the heart was enlarged both to the right and to the left. Blood pressure was 90/68 mm. Hg. A grade 4 systolic murmur was audible along the left sternal border in the fourth and fifth intercostal spaces associated with a palpable thrill. The heart sounds were of poor quality with a diastolic gallop rhythm. Râles were heard in both lungs. The liver, which was enlarged 4 inches below the costal margin, was pulsating and tender.

Laboratory studies revealed hemoglobin 13.2 Gm. per cent and hematocrit 42 volume per cent. Leukocyte count was 8,100 per cubic millimeter with a normal differential. Urinalysis was normal. In addition to the previous findings, the electrocardiogram revealed right auricular and ventricular hypertrophy with a shift of the electrical axis to the right (Fig. 2).

Roentgenograms of the chest showed moderate cardiac enlargement and pulmonary congestion (Fig. 3). Results of cardiac catheterization performed April 3, 1956, by Dr. Don W. Chapman are shown in Table I.

TABLE I

| | BLOOD | |
|---|---|---|
| | OXYGEN PER CENT SATURATION | PRESSURE (MM. Hg) |
| Superior vena cava | 70-72 | – |
| Right atrium | 74-76 | 8/3 |
| Right ventricle (low) | 88 | 16/4 |
| Right ventricle (high) | 88 | 18/8-6 |
| Main pulmonary artery | 86 | 15/8 |
| Right pulmonary artery | 85-86 | 15/7 |
| Pulmonary capillary (wedge) | – | 11/6 |

On the basis of these findings a diagnosis of left to right intracardiac shunt produced by interventricular septal defect was made and operation was recommended.

On April 5, 1956, under Pentothal ether anesthesia, a bilateral anterior thoracotomy was performed through the fourth intercostal spaces dividing the sternum at the same level. Induction of anesthesia was associated with moderate difficulty. Upon opening the pericardium a large amount of fresh, unclotted blood under considerable tension was released. The right ventricle was greatly enlarged and tense, and a systolic thrill was palpable posteriorly. The site of coronary thrombosis was identified at a point 6 cm. from the origin of the right coronary artery. A purse-string suture was placed about the auricular appendage, and after an incision was made in the auricle the left index finger was inserted. Digital exploration revealed the presence of a regurgitant jet palpable above the tricuspid valve indicating moderate tricuspid insufficiency and a strong thrill originating beneath the posterior leaflet of the valve.

Extracorporeal circulation based upon the reduced flow principle was employed to temporarily by-pass the heart after the method of Lillehei.[6] The patient's body weight was 68 Kg., and a flow of approximately 2,000 c.c. per minute (30 c.c. per kilogram of body weight per minute) was maintained using a Sigmamotor pump. A modified DeWall bubble oxygenator was used, and defoaming of the blood was accomplished with an antifoaming agent.[2] Heparin 100 mg. (1.5 mg. per kilogram of body weight) was injected into the right atrium prior to the cannulations. The superior and inferior venae cavae were cannulated to remove venous blood returning to the heart, and the right subclavian artery was cannulated to return oxygenated blood to the arterial system.

With the pump-oxygenator functioning at the calculated rate, inflow occlusion was obtained by tapes around the venae cavae. An 8 cm. right ventriculotomy incision was made on the anterior cardiac surface. Beneath the posterior leaflet of the tricuspid valve, attenuation and destruction of the posterior ventricular wall were demonstrated producing aneurysmal dilatation. The defect was visible beneath the posterior leaflet of the tricuspid valve (Fig. 4, *A*), and in order to expose the entire circumference of the defect, 2 papillary muscles of the tricuspid valve were divided and the leaflet was retracted upward (Fig. 4, *B*).

The defect measured at least 3 times 2 cm. in diameter and the edges were composed of satisfactory tissue for suturing. Repair was accomplished with 5 interrupted 3-0 black silk sutures incorporating a pad of polyvinyl sponge (Ivalon) of approximately the same size to plug the defect (Fig. 4, *C*). The papillary muscles were reattached with figure-of-eight sutures, and the ventriculotomy incision was closed with a continuous black silk suture (Fig. 4, *D*). When the occluding tapes about the venae cavae were released, cardiac action resumed and shortly thereafter the blood pressure was 110/80 mm. Hg.

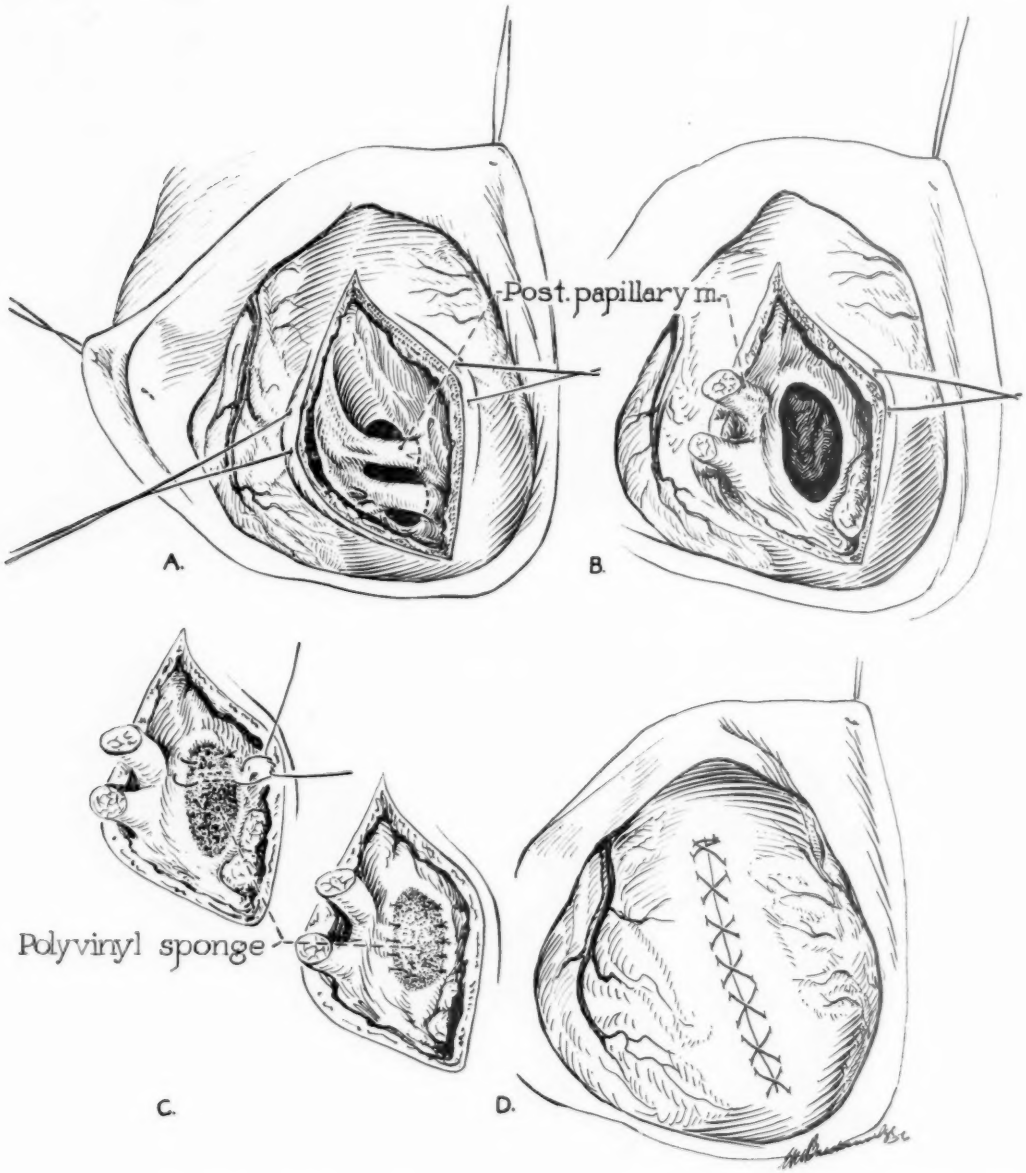


Fig. 4.—Drawings showing method of repair of defect in interventricular septum secondary to myocardial infarction. With the right ventricle opened, the 3 × 2 cm. defect may be seen in *A* partially covered by the posterior leaflet of the tricuspid valve and papillary muscles. In *B* the defect is completely exposed after dividing the papillary muscles. The method of repair is demonstrated in *C* using interrupted silk sutures and incorporating a polyvinyl (Ivalon) sponge. In *D*, the ventriculotomy incision is repaired with a continuous silk suture.

The right ventricle was reduced in volume and the thrill was eliminated. Excision or plication of the thin-walled aneurysm on the posterior surface of the right ventricle was considered but not done, and the pericardial sac was sutured loosely to permit free drainage into the pleural space. Soon after closure of the thoracotomy incision, the patient regained consciousness. Protamine sulfate was not used to counteract the heparin, but transfusions of fresh citrated blood were administered and no excessive bleeding occurred.

During the first 36 hours after operation the patient was oliguric and his condition appeared to become worse gradually. On April 7, 1956, serum sodium determination was 120 meq. per liter, chlorides 87 meq. per liter, and blood urea nitrogen was 63 mg. per cent. Because of labored respiration and cyanosis, a tracheostomy was performed and the Halliburton apparatus was attached for controlled positive pressure insufflation of the lungs with oxygen. As sodium chloride 5 per cent solution was infused slowly intravenously, his condition dramatically improved and urinary output improved steadily. Hydrocortisone and later ACTH were administered to support adrenal function and were maintained throughout his convalescence.

The patient improved remarkably during the ensuing few weeks, and blood pressure remained about 120/80 mm. Hg although a soft precordial systolic murmur persisted over the lower sternum. About 4 weeks after operation the murmur began to increase in intensity. Separation of the sternal wound occurred and a secondary closure was performed. Cardiac failure recurred about 6 weeks after operation, and in spite of vigorous treatment the patient died on May 20, 1956.

Autopsy revealed atelectasis of the right lower lobe and fibrinous pleurisy and partial collapse of the left lung. The cardiotomy incision was healed and a dense fibrinous pericarditis was present. The polyvinyl sponge was still attached in the septal defect and endothelialization of the sponge was present. One suture at the upper angle of the sponge had torn out and a 0.5 cm. opening was present between the left and right ventricles. The two papillary muscles which had been resutured to the septum were intact and firmly healed.

## DISCUSSION

Rupture of the posterior apical portion of the interventricular septum in this patient was secondary to thrombosis of the right coronary artery 6 cm. from its origin. Duration of the septal perforation prior to operation was approximately 11 weeks during which period cardiac decompensation was only partially controlled by vigorous medical treatment. It is noteworthy that death from rupture of the interventricular septum is usually not sudden but often delayed for at least several hours or days, thus providing the opportunity to attempt surgical repair in many of these cases. Accordingly, emphasis may be placed upon early diagnosis, vigorous treatment of cardiac decompensation, and preparation for prompt operation. Diagnosis can be confirmed by cardiac catheterization as in this case, yet as pointed out by others catheterization may fail to demonstrate the presence of a shunt[7] and may not be necessary in all instances.

Most septal perforations secondary to infarction are in the muscular portion near the apex and may be single or multiple with considerable variation in size. One may question the feasibility of surgical repair of such lesions on the grounds that local necrosis of the septal myocardium adjacent to the perforation may prevent successful closure and healing of the defect. Undoubtedly in some extensive infarctions which progress rapidly to septal perforation and death, the septum may be unsuitable for repair. On the other hand,

the more extensive collateral circulation of the interventricular septum in comparison to the external ventricular surface probably promotes more rapid healing in this location. Furthermore, the defect which causes death may not be large and in those patients surviving the first week, reparation has usually commenced. In this patient the rim of tissue surrounding the perforation was surprisingly firm covered by a thin layer of relatively smooth fibrin, and the sutures showed no tendency to tear out. Of course, whether or not subsequent healing will occur under these circumstances remains to be proved. Direct suture of small defects may be preferable to avoid possible complications resulting from use of a foreign body, but in large defects a plastic sponge may be desirable to plug the defect without producing excessive tension on the sutures.

On the basis of the experience in this case one may speculate that other serious complications of myocardial infarction, such as ventricular rupture with pericardial tamponade, ventricular aneurysm, and ruptured papillary muscle, may also be amenable to surgical treatment utilizing temporary extracorporeal circulation. Thus, the physician apparently faces a new challenge in selecting those patients for possible salvage by operation who have sustained an acute myocardial infarction and in whom death is almost inevitable due to cardiac dysfunction produced by localized destruction of myocardium.

## SUMMARY

Spontaneous perforation of the interventricular septum is usually a fatal complication of acute myocardial infarction. Medical treatment is ineffective and prolongs life only briefly. Death in almost 50 per cent of cases occurs more than one week after perforation providing an interval for diagnosis by cardiac catheterization and surgical intervention.

In a 49-year-old patient, closure of an acquired septal perforation of 11 weeks' duration resulting from myocardial infarction was accomplished utilizing a temporary cardiac by-pass. Diagnosis before operation was confirmed by cardiac catheterization. Although death from technical reasons occurred 45 days later, this experience suggests that direct surgical correction of this and other complications of acute myocardial infarction may be feasible.

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# TRANSPOSITION OF THE GREAT VESSELS CORRECTED BY MEANS OF ATRIAL TRANSPOSITION

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MANY techniques have been devised during the past few years for the surgical correction of transposition of the great vessels, none of which have been successful in the complete correction of this congenital cardiac anomaly. Hanlon and Blalock,[5] in 1948, were the first to attempt alleviation of this condition by performing various shunt operations to increase the intermixing of the blood. These patients were only moderately improved and their arterial oxygen saturation generally remained below 75 per cent. Lillehei and Varco,[7, 8] in 1953 and 1955, reported their experience in the partial transposition of the venous return. Of 32 patients so treated, there has been some palliation in 7 survivors. Baffes,[2] in 1956, reported a similar experience employing a homologous graft to transpose the inferior vena cava and right pulmonary veins. Mustard and associates,[9] in 1954, attempted to retranspose the pulmonary artery and aorta, utilizing an extracorporeal circulation (monkey lungs). In the same year we[4] reported a cross-shunting technique by which the aortic and pulmonary valves could be by-passed by means of valved plastic shunts between the ventricles and great vessels. During the same year, Björk and Bouckaert[3] employed homologous arterial grafts experimentally to criss-cross the circulation in dogs. In 1955, Albert[1] reported the experimental use of the atrial septum in cross-shunting the circulation at the atrial level, and in the same year we[6] reported a technique to retranspose the aorta and pulmonary artery. This latter technique was employed in 3 infants unsuccessfully. All of the infants died postoperatively from pulmonary edema, congestion, and hemorrhage from what was felt to be the inability of the high resistance bed of the pulmonary circulation to further adapt itself to the acutely increased pressure from the dominant hypertrophied right ventricle.

From this experience it was concluded that the ventricular system and arterial outflow tracts must remain the same and that if success were to be achieved, the venous inflow must be reversed. It was felt that the palliation afforded by the partial transposing of the venous return described by Lillehei and Varco[7] was inadequate and that the use of the atrial septum as described by Albert[1] was impractical clinically. As a consequence, a technique was devised that appears to have potentialities even though it has not been successful in

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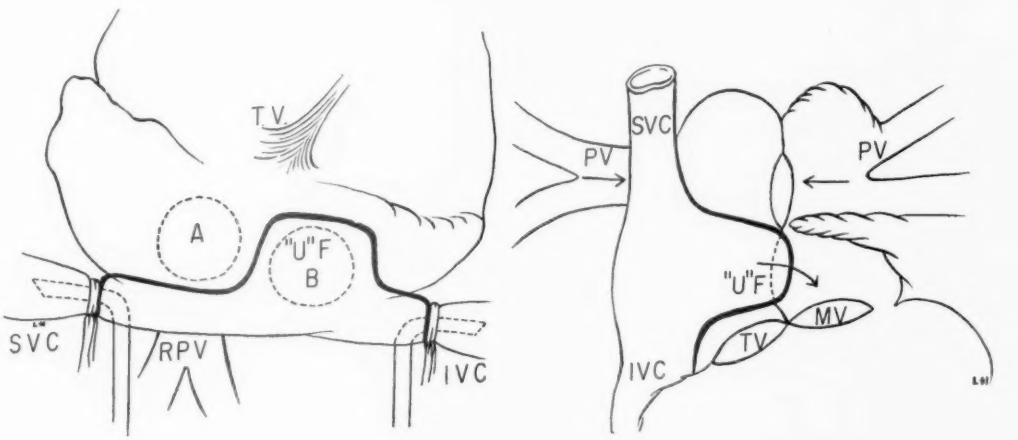
the 2 patients upon whom it has been employed. It has also been felt that such infants would have the best chance of survival if the associated defects are corrected at the time of transposing the circulation.

The technique as employed entails the use of a pump-oxygenator to maintain circulation and oxygenation during the operative procedure. After the child is put on the extracorporeal circulation, a right ventriculotomy is performed. A pulmonary stenosis, if present, can be corrected, following which the ventricular septal defect is repaired and the ventriculotomy is closed. An incision is then made in the right auricular wall along the projected course of the superior vena cava. This incision is extended to include a U-flap of the auricular wall just proximal to the inferior vena cava. The superior vena cava is then reconstructed down to the U-flap. Two large openings are then made in the auricular septum. The left auricular wall is then grasped on the valvular side of the ostia of the pulmonary veins and sutured about the cephalad opening in the auricular septum. This directs the pulmonary venous drainage to the right side. The U-flap to which the superior and inferior venae cavae communicate is then sutured about the caudal opening in the auricular septum in such a manner that the stoma of the coronary sinus is also included so that all of the systemic venous return is directed toward the remaining chamber of the left auricle (Figs. 1 and 2). The right auricular appendage is then opened and used to reconstruct the lateral wall of the right atrium.




*A.* *B.*

Fig. 1.—*A*, Diagrammatic sketch of right atrium viewed laterally and demonstrating the incision in the atrial wall and the openings made in the atrial septum. (a) Cephalad opening in auricular septum to which pulmonary veins are anastomosed. (b) Caudad opening in auricular septum through which vena caval drainage empties into left auricle. *B*, Diagrammatic sketch of atrial communications as viewed from above, demonstrating the transposition within the auricles of the venous return to the ventricles. See text.

Two infants have been operated upon by this technique. The first infant was 19 months of age and weighed 14 pounds. The ventricular septal defect in this child was not closed. The total extracorporeal by-pass time was 63 minutes. The blood serum hemoglobin increased from 49.5 mg. per cent preoperatively to 154.5 mg. per cent postoperatively. The child's color following operation was excellent and he responded immediately. The initial postoperative roentgenogram of the chest showed both lungs well expanded. To insure

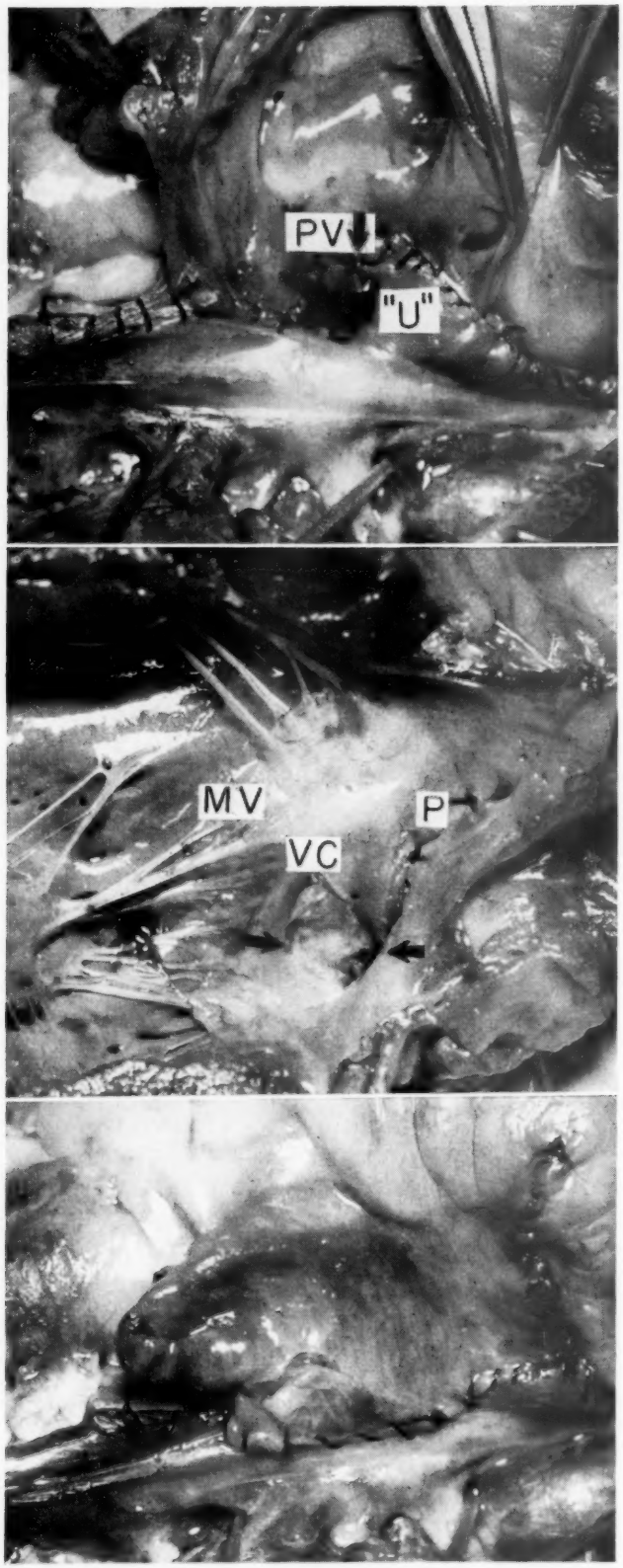
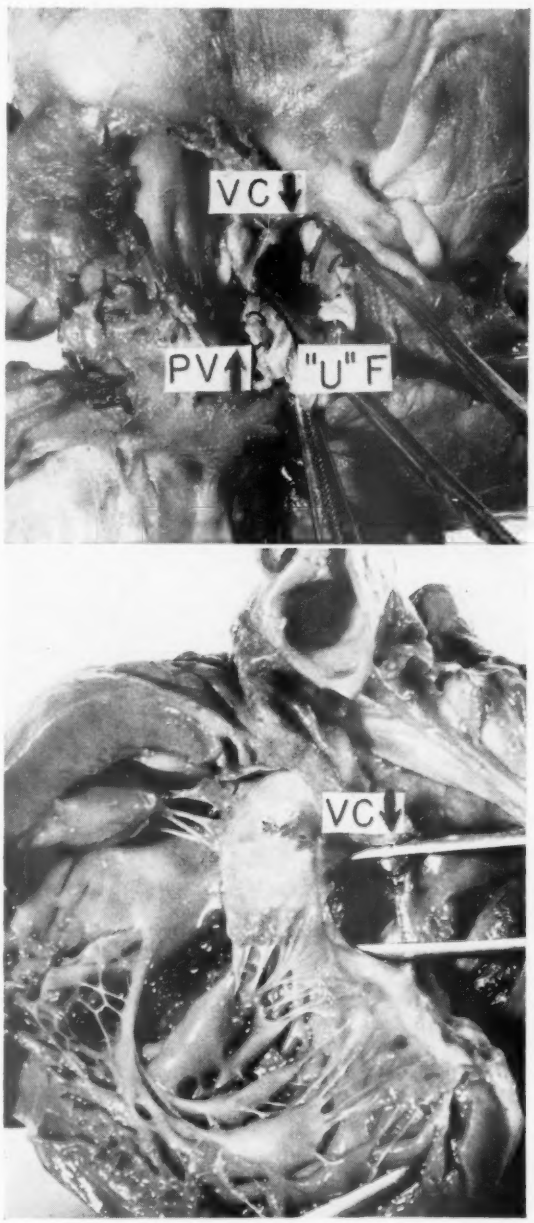



Fig. 2.—*A*, Photograph of right auricle of a dog demonstrating atrial transposition of venous return. (PV) Pulmonary venous drainage stoma communicating with right auricle. ("U") U-flap of auricular wall sutured to caudal stoma in atrial septum and directing systemic venous return to left auricle. *B*, Photograph of dog's heart viewed from the left. (VC) Vena caval stoma communicating with left auricle just proximal to mitral valve. Arrows demarcate the opening which was filled with cotton plug. (P) Partition within left auricle resulting from suturing left auricular wall on the valvular side of the ostia of the left pulmonary veins to the cephalad stoma in the atrial septum. (MV) Mitral valve. *C*, Photograph of right auricle of a dog's heart following reconstruction of the auricular wall.

an adequate airway in this very weak infant, the intratracheal tube was left in place. Approximately 3 hours postoperatively the child became increasingly cyanotic and expired about one hour later. The only finding of significance at necropsy was the presence of total atelectasis of the left lung. It was felt that the intratracheal tube had inadvertently slipped into the right main stem bronchus thereby occluding the left lung, resulting in atelectasis.

*A.*




*B.*

Fig. 3.—*A*, Photograph of necropsy specimen demonstrating pulmonary venous drainage stoma (PV) and U-flap partially detached to reveal underlying stoma (VC) for vena caval return to left side. *B*, Photograph of necropsy specimen demonstrating vena caval stoma (VC) as viewed from left side.

The second patient was a child 3 years of age. The total by-pass time was one hour and 49 minutes. After the child was put on the extracorporeal circulation, a right ventriculotomy was performed. A large ventricular septal defect was present. A stenotic bifid pulmonary valve was opened through the ventricular septal defect. The ventricular septal defect was then closed utilizing an Ivalon sponge because of its large size. The ventriculotomy was closed. The venous return within the atrial chambers was then transposed as described above. The arterial oxygen saturation immediately prior to the procedure was 22.2 volumes per cent and postoperatively was 94.1 volumes per cent. The hemolysis increased from 31 to 93 mg. per cent during the operation. The postoperative clotting time was 9 minutes. The mean femoral arterial pressure postoperatively was 86 mm./Hg. The preoperative pH was 7.35 and 7.33, postoperatively. The child had a heart block postoperatively with a ventricular rate of 60, probably resulting from the placement of a suture too deeply in the tissue just above the coronary sinus. However, her general status remained good until the following day when the heart rate progressively decreased over a period of 2 to 3 hours, and death ensued 25 hours postoperatively. The necropsy findings showed a satisfactory surgical transposition of the venous return within the auricles. (Fig. 3.) The exact cause of the heart block could not be ascertained but undoubtedly resulted from some interference with the conduction system.

Though this technique for the correction of transposition of the great vessels has not as yet been employed successfully, its potentialities are sufficiently encouraging to be reported that others in the field may have the opportunity to employ it with success.

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# COMPARATIVE EXPERIMENTAL STUDY OF AORTIC GRAFTS

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THE need for further information about vascular grafts and substitutes has become an urgent problem as a consequence of the development of satisfactory techniques for the excisional therapy of aortic aneurysms, the realization that aneurysms and arteriovenous fistulas of peripheral arteries should be treated in such a way as to maintain or restore the continuity of blood flow through the affected artery, and the use of by-pass grafting procedures for obstructive arterial lesions. Though the results, both in the experimental laboratory and in patients, with the use of arterial homografts have not been entirely satisfactory, they have proved altogether most gratifying. The available data concerning heterografts are conflicting.[3, 10, 11] Since the original study by Voorhees, Jaretzki, and Blakemore[15] of aortic prostheses fashioned from Vinyon N fabric, a number of experimental and clinical studies have demonstrated that a variety of plastic materials can be used successfully for replacement of arterial segments.[1, 2, 5-9, 12-15]

For some years we have been interested in these problems and particularly in plastic grafts. The first study was concerned with the use of a very thin nylon cloth which had been found to work satisfactorily in the experimental closure of defects of the cardiac septa. Because blood initially passed through this material very readily, it was rendered impervious by heat fusion with polythene or by coating it with methyl methacrylate. The fused nylon and polythene gave reasonably good results. Grafts of this material a centimeter in diameter placed in the aortas of dogs worked well. Grafts of smaller diameter were attended by a significant incidence of thrombosis. In human patients the same material proved satisfactory for aortic and aortic bifurcation replacement. The methyl methacrylate coated nylon was less successful in experimental canine aortic grafting. One patient in whom such a graft was used for aortic bifurcation replacement has done well for a period of 2 years. In order to gain more knowledge about various plastic materials, another experimental study was undertaken in which freeze-dried aortic homografts were compared with prostheses made of various plastic materials. The plastic grafts were all sewed together with a sewing machine, were equal in diameter, and were used to replace 5 cm. segments excised from the thoracic aorta. This

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study, which included few long-term observations, revealed the fact that very good results were obtained from the homografts and from grafts made of a nylon filter fabric. Grafts made of material constructed by heat fusion of a very thin layer of polythene between 2 thin layers of nylon cloth, though generally satisfactory, were not as successful. Grafts constructed by heat fusion of a single layer of nylon and polythene, the polythene being on the exterior, were less satisfactory. The poorest results were obtained with Vinyon N grafts. Though some of the animals had excellent results, there was a rather high incidence of poor results both from bleeding through the graft and from thrombosis. Somewhat longer follow-up studies on this series of animals, together with our initial observations with the braided tubular grafts of Edwards and Tapp[7] were subsequently reported. It is the purpose of this paper to describe more extended observations upon these materials, together with some preliminary studies of heterografts.

## MATERIALS AND METHODS

Nine types of grafts were used. The arterial homografts were removed from dogs without sterile precaution, cleaned of the adjacent areolar tissue, bathed for one hour in liquid ethylene oxide, frozen in pyrex tubes, submerged in a dry ice-acetone bath, lyophilized, and stored in sealed tubes filled with nitrogen. Before they were used they were reconstituted by immersion for one hour in isotonic saline solution containing penicillin and streptomycin. A second type of graft was made of the previously described nylon filter fabric, an off-balance taffeta constructed of multifilament highly twisted yarn strands with a warp count of 232 and a filling count of 96. The yarn is 70 denier nylon with 35 turns per square inch in length. The cloth was used as it was received from the manufacturer without previous washing or other treatment.* The third material was the same nylon filter fabric graft which had been thoroughly washed in a detergent before construction of the grafts. The fourth material was prepared by fusing a thin film of polythene† between 2 sheets of finely woven nylon cloth,‡ as previously described. A single layer of the same nylon fabric was commercially fused with the same polythene film by impulse sealing for the fifth type of graft.§ The sixth was a Vinyon N cloth like that originally used by Voorhees, Jaretzki, and Blakemore.‖ All of the plastic materials were made into grafts by sewing the cloth into tubular shape with an ordinary sewing machine using a fine needle and fine nylon thread placed 25 stitches per inch. All, save the Vinyon N grafts, were sterilized by autoclaving for 10 minutes at 250° F. and 20 pounds pressure. The Vinyon N grafts were boiled for 15 minutes. All of these plastic grafts were 0.78 cm. in diameter and 5.4 cm. in length. The nylon tubular grafts were braided tubes

*HT-5F nylon filter fabric. Equipment Development Company, Inc., 368 Bloomfield Avenue, Montclair, N. J.

†PE = 2600 Polythene film, 0.0015 inch thickness. Clay-Adams Company, Inc., 308 Washington Street, Chicago.

‡24 F nylon fabric. The Stehli Company, Inc., 1372 Broadway, New York, N. Y.

§Through the courtesy of Dr. C. E. Irion, Ben-mont Papers, Inc., Binnington, Vt.

‖Supplied by Mr. T. P. Mulligan, Carbide and Carbon Chemicals Corporation, Division of Union Carbide and Carbon Corporation, 30 East 42nd St., New York, N. Y.

of large porosity treated with formic aid in order to solve the problem of easy frayability, crimped in an accordion-like manner to permit bending without wrinkling, and siliconed in order to prevent excessive blood loss through the material.* They, too, were 5.4 cm. in length and were either 0.8 or 0.6 cm. in diameter. They were sterilized by autoclaving. The additional grafts were heterografts. Pig aortas and the carotid arteries of cattle were used. After being removed from the animal, they were placed in 70 per cent by weight alcohol solution and prior to implantation were immersed in physiologic saline with penicillin and streptomycin for one hour.

The grafts were implanted into the thoracic aorta after a 5 cm. segment had been removed. All operations were done aseptically under moderate hypothermia. The braided nylon grafts were sutured in place with simple over-and-over continuous sutures. Continuous everting mattress sutures were used in all other types of grafts. In most of them the everted edges were caught with a simple over-and-over suture after placement of each mattress stitch (Fig. 1). The pleura was carefully closed over the grafted area.

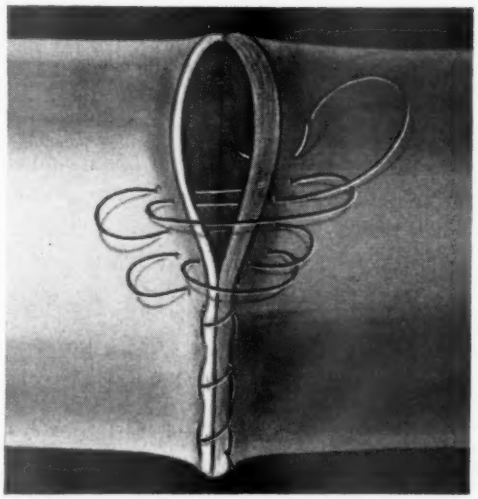

Fig. 1.—Drawing showing method of suture. (From Harris et al., Arch. Surg. 71: 449, 1955.)

In each case at the time of post-mortem examination, the grafts, together with an adjacent segment of the aorta above and below, were removed. They were washed thoroughly with physiologic saline. A few were opened in the fresh state. Most of them were distended with formalin solution after ligating the aorta above and below and were opened subsequently after fixation. Photographs and microscopic sections were obtained.

## OBSERVATIONS

The results described are a compilation of the previously recorded observations and those made subsequently. Only data are included from animals in which the graft has been inspected at the time the animal was sacrificed or

*Supplied by Mr. J. S. Tapp, Research Department, The Chemstrand Corporation, Decatur, Ala.

died. A very few cases in which an obvious technical error was made have been excluded from consideration. The results have been classified in this manner. They were considered excellent when the graft was widely patent, had a thin, smooth lining without evidence of intramural thrombi or degenerative changes and without external clots or constriction. They have been considered good when the graft was widely patent with an essentially smooth lining but with minimal erosion, minimal degenerative changes or very tiny intramural thrombi, and with no external constriction but perhaps with very small external thrombi. They were considered satisfactory if there was a functional aortic pathway in spite of a somewhat narrowed lumen or a very slightly dilated lumen. Some had a rough, irregular lining membrane as the result of mural thrombi, excessive fibrinous reaction, or marked degenerative changes. Others had some external constriction either from thrombi or from excessive fibrinous reaction. The results were considered poor if the graft failed as a conduit from exsanguination, disruption, or an occluding thrombus, or when moderate or marked dilatation of the graft was present.

The results with the various types of grafts are listed in Tables I to IX. In Table X the data are compared. The best results were obtained with the washed nylon filter fabric, the braided tubular grafts, and homografts. Seventy-three per cent of the washed filter fabric grafts were regarded as excellent, 27 per cent as good. None was only satisfactory or poor. Eighty-seven per cent of the braided tubular grafts were excellent, while a single graft was considered a good result and another poor. Seventy per cent of the homografts were excellent, 20 per cent good. A single graft was thought satisfactory and another poor. Slightly less good results were obtained with the unwashed nylon filter fabric. Forty-one per cent were excellent, and 47 per cent were good.

TABLE I. RESULTS WITH HOMOGRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 4 | 0 | 0 | 1 |
| 51 to 100 | 2 | 1 | 0 | 0 |
| 101 to 150 | 2 | 0 | 0 | 0 |
| 151 to 200 | 2 | 1 | 0 | 0 |
| 201 to 250 | 1 | 1 | 0 | 0 |
| 251 to 300 | 0 | 1 | 0 | 0 |
| 301 to 400 | 0 | 0 | 0 | 0 |
| 401 to 500 | 3 | 0 | 1 | 0 |
| Total | 14 | 4 | 1 | 1 |

TABLE II. RESULTS WITH WASHED NYLON FILTER FABRIC GRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 3 | 3 | 0 | 0 |
| 51 to 100 | 0 | 0 | 0 | 0 |
| 101 to 150 | 1 | 1 | 0 | 0 |
| 151 to 300 | 0 | 0 | 0 | 0 |
| 301 to 400 | 7 | 0 | 0 | 0 |
| Total | 11 | 4 | 0 | 0 |

A single graft was satisfactory and another poor. In these 4 groups the good and excellent results varied from 88 to 100 per cent. The grafts made by fusion of one layer of polythene between 2 layers of thin nylon gave less favorable results, 71 per cent being good or excellent and 29 per cent poor. Those

TABLE III. RESULTS WITH UNWASHED NYLON FILTER FABRIC GRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 4 | 0 | 0 | 0 |
| 51 to 100 | 1 | 2 | 0 | 1 |
| 101 to 150 | 1 | 0 | 0 | 0 |
| 151 to 200 | 0 | 2 | 1 | 0 |
| 201 to 300 | 0 | 0 | 0 | 0 |
| 301 to 400 | 1 | 4 | 0 | 0 |
| Total | 7 | 8 | 1 | 1 |

TABLE IV. RESULTS WITH BRAIDED NYLON TUBULAR GRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 2 | 0 | 0 | 1 |
| 51 to 100 | 3 | 0 | 0 | 0 |
| 101 to 150 | 2 | 1 | 0 | 0 |
| 151 to 250 | 0 | 0 | 0 | 0 |
| 251 to 300 | 2 | 0 | 0 | 0 |
| 301 to 400 | 4 | 0 | 0 | 0 |
| Total | 13 | 1 | 0 | 1 |

TABLE V. RESULTS WITH NYLON POLYTHENE—NYLON GRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 3 | 1 | 0 | 3 |
| 51 to 100 | 0 | 1 | 0 | 0 |
| 101 to 150 | 0 | 0 | 0 | 0 |
| 151 to 200 | 1 | 0 | 0 | 0 |
| 201 to 250 | 0 | 1 | 0 | 1 |
| 251 to 300 | 0 | 0 | 0 | 0 |
| 301 to 400 | 0 | 1 | 0 | 0 |
| 401 to 500 | 0 | 2 | 0 | 0 |
| Total | 4 | 6 | 0 | 4 |

TABLE VI. RESULTS WITH NYLON—POLYTHENE GRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 4 | 1 | 0 | 4 |
| 51 to 100 | 0 | 1 | 0 | 0 |
| 101 to 150 | 0 | 0 | 0 | 0 |
| 151 to 200 | 0 | 1 | 2 | 0 |
| 201 to 250 | 1 | 0 | 0 | 0 |
| 251 to 400 | 0 | 0 | 0 | 0 |
| 401 to 500 | 0 | 0 | 1 | 0 |
| 501 to 600 | 0 | 0 | 2 | 0 |
| Total | 5 | 3 | 5 | 4 |

made by fusion of a single layer of polythene and a single layer of nylon and the Vinyon N grafts were still less satisfactory, only about half yielding good or excellent results. The heterografts were the poorest.

These over-all observations reflect not only the more long-term results but the early failures as well. The relatively long-term observations are recorded in

TABLE VII. RESULTS WITH VINYON N GRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 0 | 1 | 0 | 5 |
| 51 to 100 | 1 | 0 | 1 | 0 |
| 101 to 150 | 1 | 0 | 1 | 0 |
| 151 to 200 | 3 | 0 | 0 | 1 |
| 201 to 250 | 0 | 0 | 0 | 0 |
| 251 to 300 | 1 | 0 | 0 | 0 |
| 301 to 500 | 0 | 0 | 0 | 0 |
| 501 to 600 | 0 | 1 | 0 | 0 |
| Total | 6 | 2 | 2 | 6 |

TABLE VIII. RESULTS WITH PIG HETEROGRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 0 | 1 | 1 | 0 |
| 51 to 150 | 0 | 0 | 0 | 0 |
| 151 to 200 | 0 | 0 | 0 | 1 |
| 201 to 250 | 0 | 0 | 0 | 1 |
| Total | 0 | 1 | 1 | 2 |

TABLE IX. RESULTS WITH COW HETEROGRAFTS

| AGE OF GRAFT (DAYS) | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|
| 1 to 50 | 1 | 0 | 2 | 1 |
| 51 to 100 | 1 | 0 | 0 | 0 |
| 101 to 150 | 0 | 0 | 1 | 0 |
| 151 to 200 | 0 | 0 | 0 | 0 |
| 201 to 250 | 0 | 1 | 0 | 1 |
| 251 to 300 | 0 | 0 | 0 | 1 |
| 301 to 400 | 1 | 0 | 1 | 0 |
| Total | 3 | 1 | 4 | 3 |

TABLE X. RESULTS WITH VARIOUS TYPES OF AORTIC GRAFTS

| TYPE OF GRAFT | NO. GRAFTS STUDIED | NO. WITH EXCELLENT RESULT | NO. WITH GOOD RESULT | NO. WITH SATISFACTORY RESULT | NO. WITH POOR RESULT |
|---|---|---|---|---|---|
| Homograft | 20 | 14 | 4 | 1 | 1 |
| Nylon filter fabric, washed | 15 | 11 | 4 | 0 | 0 |
| Nylon filter fabric, unwashed | 17 | 7 | 8 | 1 | 1 |
| Braided tubular nylon | 15 | 13 | 1 | 0 | 1 |
| Nylon-polythene-nylon | 14 | 4 | 6 | 0 | 4 |
| Nylon-polythene | 17 | 5 | 3 | 5 | 4 |
| Vinyon N | 16 | 6 | 2 | 2 | 6 |
| Pig heterografts | 4 | 0 | 1 | 1 | 2 |
| Cow heterografts | 11 | 3 | 1 | 4 | 3 |

Table XI. The best results were obtained with washed nylon filter fabric and braided nylon tubular grafts. Seven of the former, ranging in age from 315 to 376 days, were all excellent. Six of the latter, varying in age from 275 to 352 days, were also all excellent. The outcome was not as good in the case of homografts. Though some were excellent after almost 500 days of implantation, a number, 260 days old or older, had minimal or marked degenerative changes.

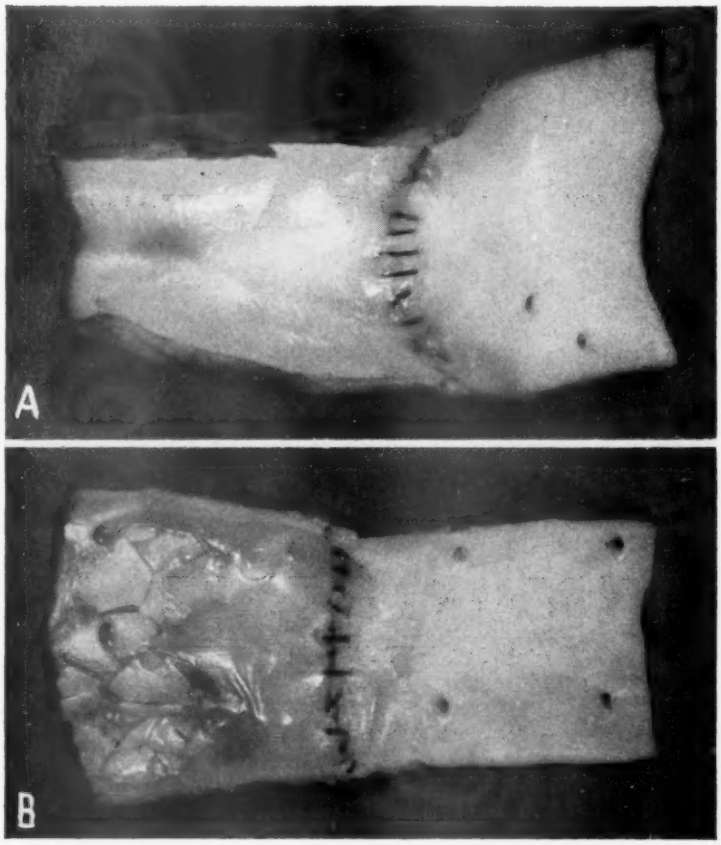


Fig. 2.—Photographs of portions of homografts and adjacent aorta. *A*, Specimen from Dog 637 after 471 days of implantation. The graft was in excellent condition. *B*, Specimen from Dog 621 after 490 days of implantation. Marked degenerative changes with extensive calcification are evident.

Some had calcification. The unwashed nylon filter fabric grafts tended to exhibit minimal roughening of the lining membrane. There were only 2 Vinyon N grafts. One 298 days old was thought excellent, one 544 days old good. The grafts of 2 layers of nylon with polythene in between included one 222-day-old grafts with complete luminal occlusion from a distal thrombosis. The others were good with some roughening of the lining membrane. Results from grafts made of a single layer of nylon fused with a layer of polythene were less satisfactory principally because of the common occurrence of thrombi between the layers of the graft causing partial constriction of the lumen. The few cow

TABLE XI. RELATIVELY LONG-TERM OBSERVATIONS WITH VARIOUS TYPES OF AORTIC GRAFTS

| TYPE OF GRAFT | GRAFTS 200 OR MORE DAYS OLD | | | | GRAFTS 300 OR MORE DAYS OLD | | | |
|---|---|---|---|---|---|---|---|---|
| | NO. WITH EXCELLENT RESULTS | NO. WITH GOOD RESULTS | NO. WITH SATISFACTORY RESULTS | NO. WITH POOR RESULTS | NO. WITH EXCELLENT RESULTS | NO. WITH GOOD RESULTS | NO. WITH SATISFACTORY RESULTS | NO. WITH POOR RESULTS |
| Homograft (1) | 4 | 2 | 1 | – | 3 | – | 1 | – |
| Nylon filter fabric, washed (2) | 7 | – | – | – | 7 | – | – | – |
| Nylon filter fabric, unwashed (3) | 1 | 4 | – | – | 1 | 1 | – | – |
| Braided tubular nylon (4) | 6 | – | – | – | 4 | – | – | – |
| Nylon-polythene-nylon (5) | – | 4 | – | 1 | – | 3 | – | – |
| Nylon-polythene (6) | 1 | – | 3 | – | – | – | 3 | – |
| Vinyon N (7) | 1 | 1 | – | – | – | 1 | – | – |
| Cow heterografts (8) | 1 | 1 | 1 | 2 | 1 | – | 1 | – |

**Ages of grafts in days:**

(1). 230, 250, 260, 471, 485, 490, 495
(2). 315, 315, 329, 335, 340, 372, 376
(3). 210, 235, 240, 330, 405
(4). 275, 290, 308, 308, 310, 352
(5). 222, 238, 400, 405, 494
(6). 217, 466, 525, 541
(7). 298, 544
(8). 203, 245, 265, 325, 339

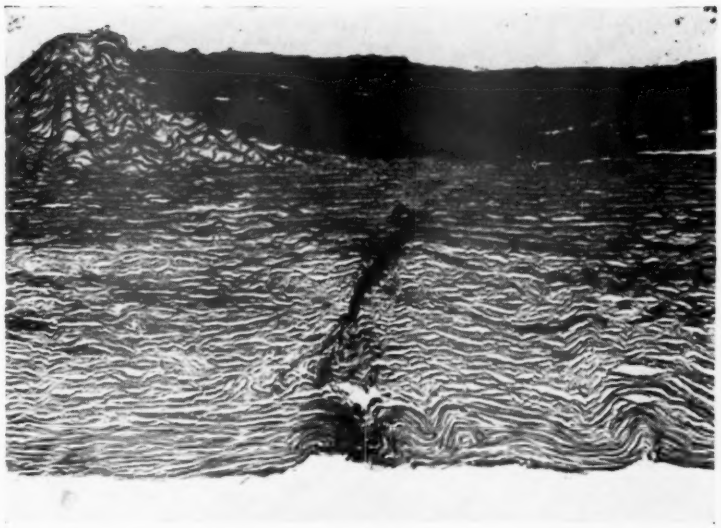

Fig. 3.—Photomicrograph of homograft from Dog 621, 490 days old. The extensive calcification is seen. The elastic fibers are fragmented.

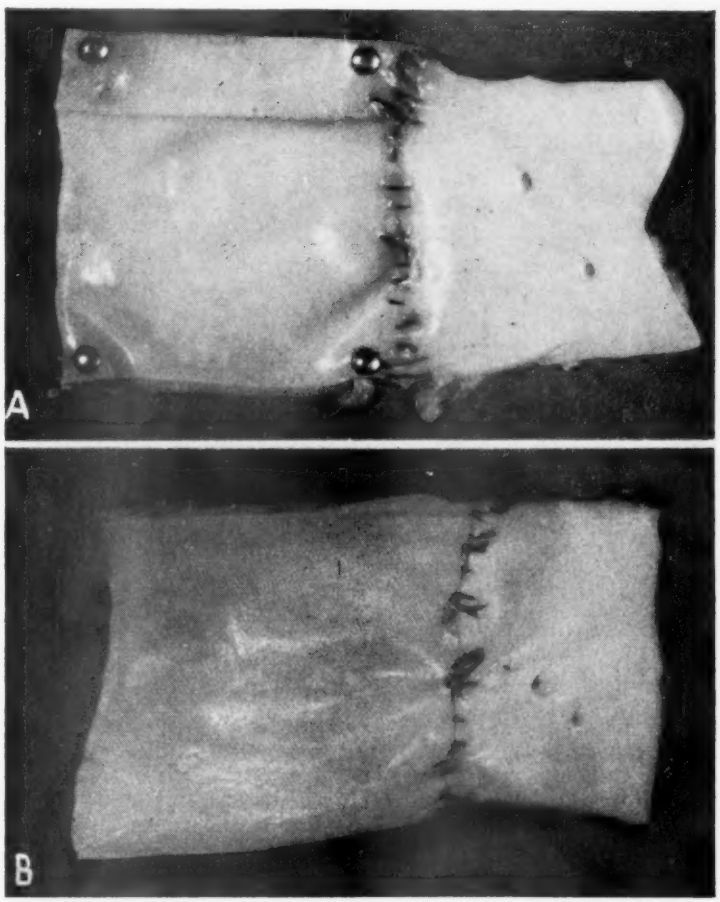


Fig. 4.—Photographs of portions of washed nylon filter fabric grafts and adjacent aorta. *A*, Specimen from Dog 19, 372 days old. *B*, Specimen from Dog 29, 329 days old. The lining membrane is smooth and glistening.

heterografts were rather poor. Though one graft 203 days old had only minimal degenerative changes and one 325 days old was considered excellent, 2 grafts 245 and 265 days old, respectively, showed considerable dilatation and one 339 days old had an extensive mural thrombus.

The more long-term results with homografts were somewhat less satisfactory than the over-all observations. The majority were excellent (Fig. 2, *A*),

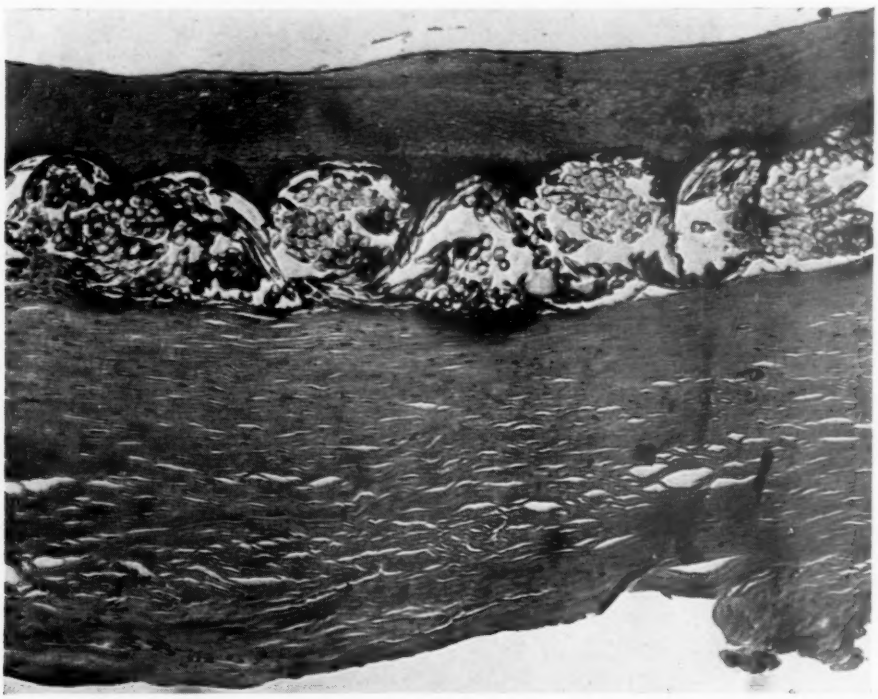

Fig. 5.—Photomicrograph of washed nylon filter fabric graft from Dog 41, 315 days old. The strands of the fabric lie between a thin, inner fibrocellular coat lined with flat cells and a thicker outer fibrous coat. Fibroblasts have grown in between strands of the fabric.

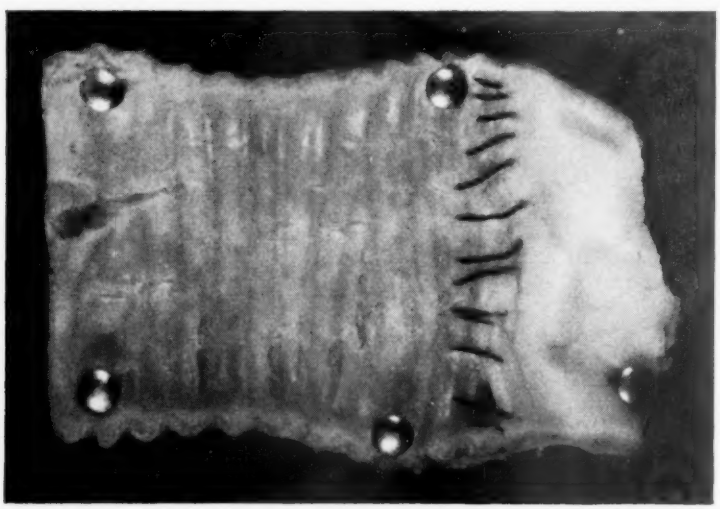

Fig. 6.—Photograph of portion of braided nylon tubular graft from Dog 53, 308 days old. The cracks visible are artifacts made by opening the fixed specimen. The ridging of the lining membrane is seen. It is otherwise smooth and glistening.

but one graft 250 days old had a small mural thrombus; another 260 days old showed minimal degenerative changes; and one 490 days old exhibited extensive degenerative changes and calcification (Fig. 2, *B*). Microscopic studies of these grafts show the same features which have previously been described well by others. In some no degenerative changes were seen and the elastic layer was well preserved. In others there were extensive degenerative changes with calcification (Fig. 3) and the elastic fibers were fragmented.

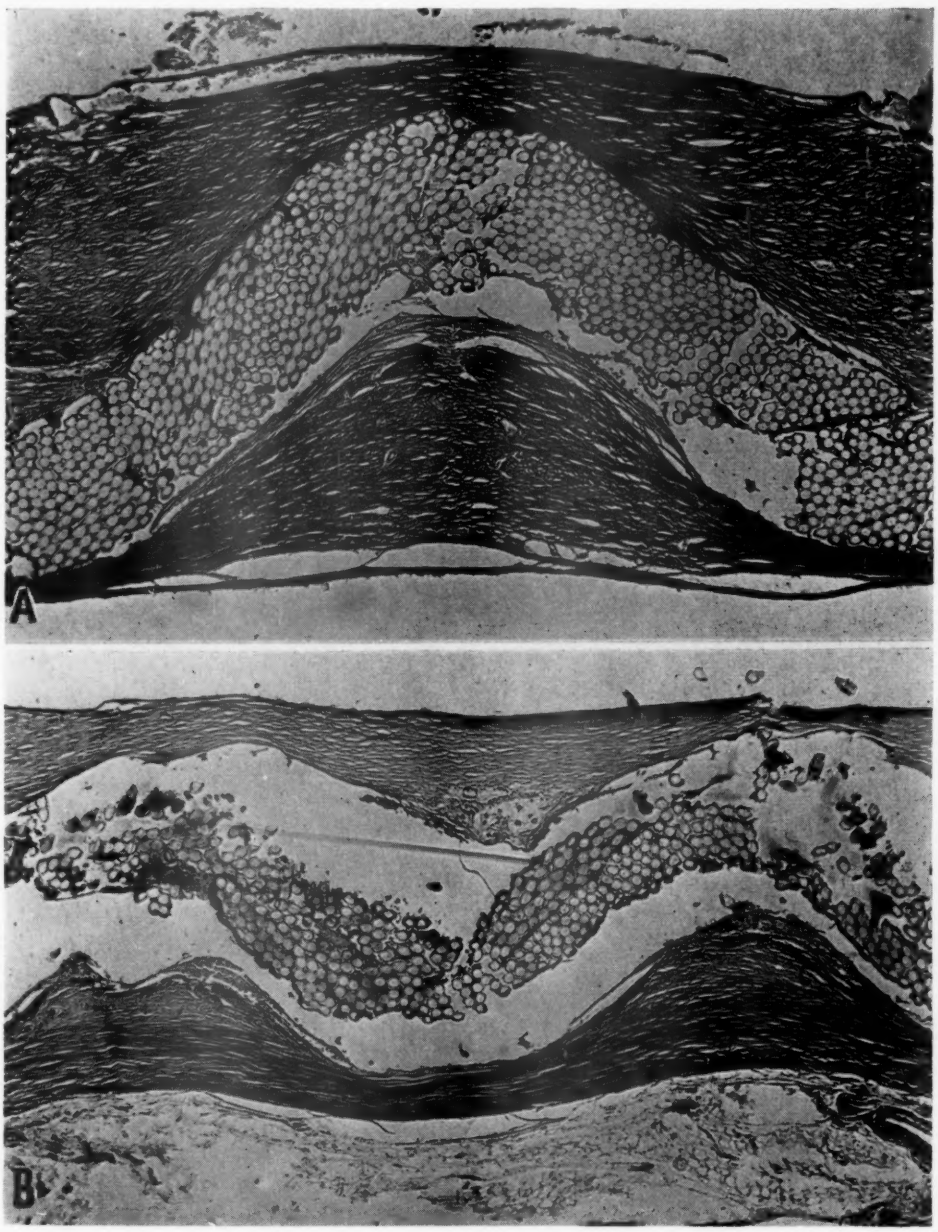


Fig. 7.—Photomicrographs of braided nylon tubular grafts from Dogs 49 (*A*) and 69 (*B*). The former was implanted 148 days, the latter 290 days. The separation of layers is an artifact due to difficulty in sectioning. It is seen that the inner layer is alternately thin and thicker as the crimped plastic bends toward or away from the lumen and that the opposite is true of the outer fibrous layer.

The washed nylon filter fabric grafts gave excellent results. Three of the grafts after short periods of implantation were considered only good because of minimal extrinsic thrombi. One 4 months old showed the same imperfection. All 4 had a thin, smooth lining and a widely patent lumen. The rest of the grafts were thought to be excellent (Fig. 4). Microscopically they showed excellent incorporation of the strands of nylon in the new fibrous aorta (Fig. 5). On the inside was a very thin, smooth fibrocellular lining membrane covered with flat cells. The outer fibrous layer was somewhat thicker.

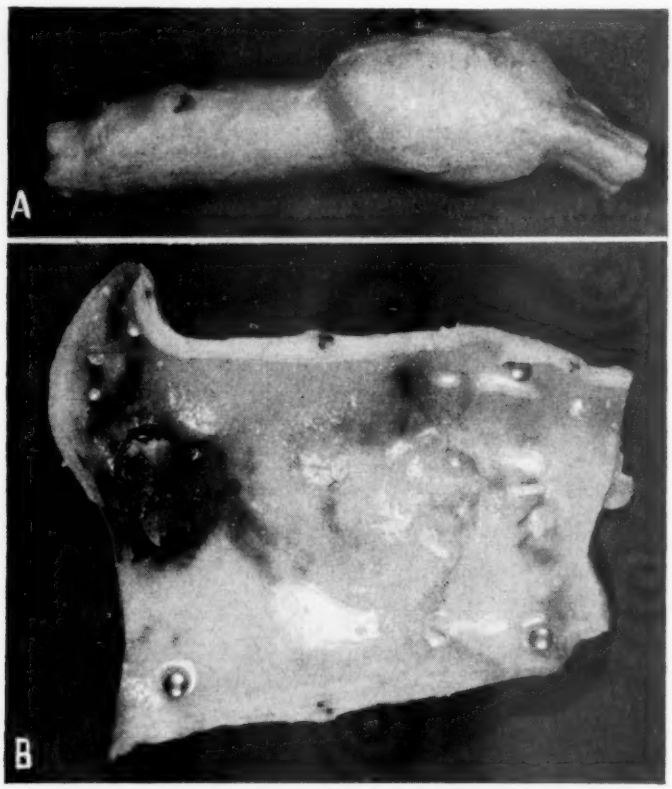


Fig. 8.—Photograph of typical pig heterograft. *A*, External appearance of specimen from Dog 566, 230 days old, showing aneurysmal dilatation. *B*, Portion of same specimen opened, showing degenerative changes and mural thrombus.

The unwashed nylon filter fabric grafts were not quite so good. However, except for one poor and one satisfactory result, these grafts differed from the washed nylon grafts principally in that minimal roughening of the lining membrane and small mural thrombi were not infrequently observed. Their microscopic appearance has been previously described and is similar to that of the washed nylon filter fabric grafts except for a somewhat thicker inner fibrocellular layer.

The braided nylon tubular grafts yielded results comparable to those grafts made of washed nylon filter cloth. Except for one graft which became occluded early with a thrombus and another 5 months old in which there was a very

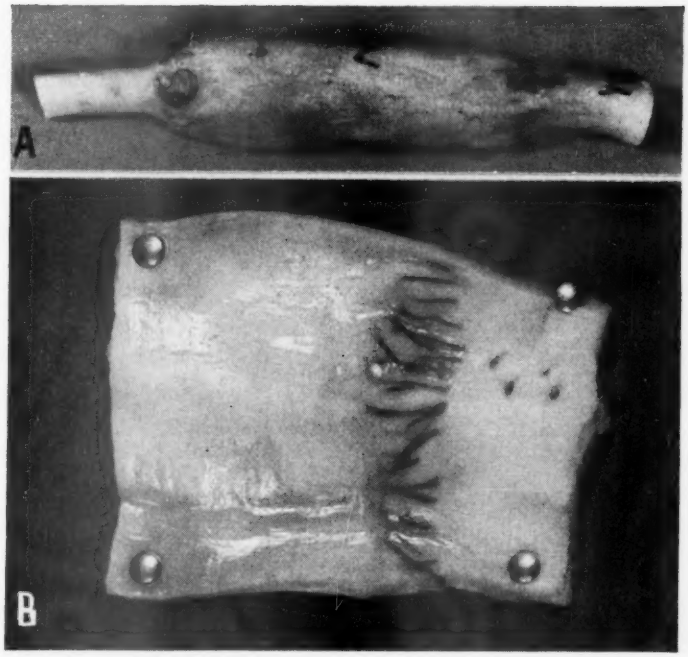


Fig. 9.—Photographs of cow heterografts. *A*, External appearance of specimen from Dog 102, 265 days old, showing diffuse dilatation. *B*, Portion of specimen from Dog 31, 325 days old. Grossly the graft was in excellent condition.

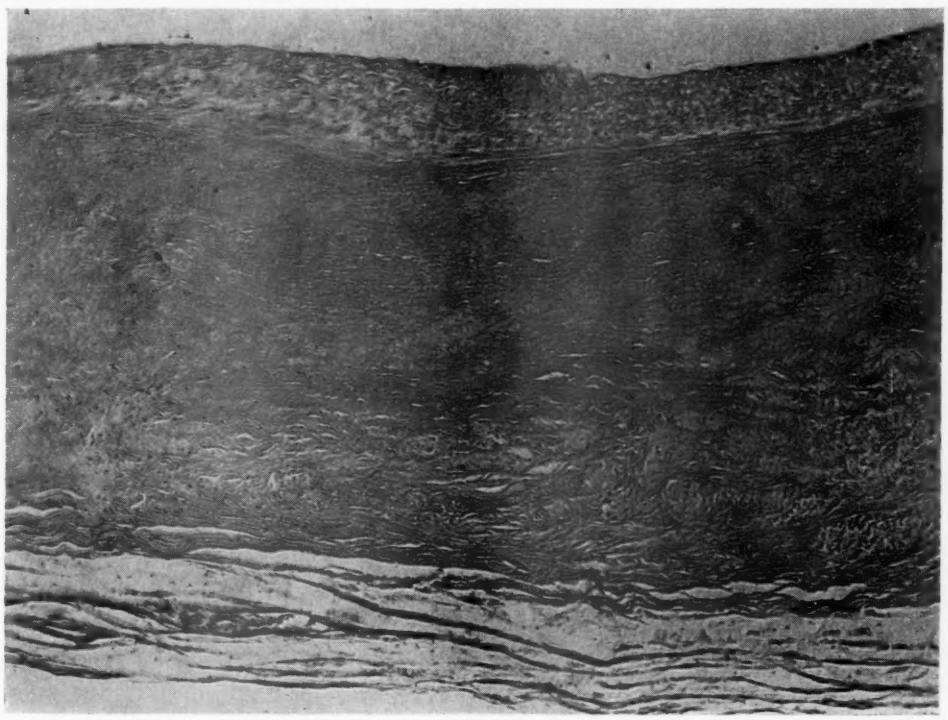

Fig. 10.—Photomicrograph of cow heterograph from Dog 31, 325 days old. Though this was grossly the best heterograft of the entire group, microscopically the original graft appears principally as dead acellular material with only a few apparently viable fibroblasts present. There is a thin inner fibrocellular layer and a thin loose outer fibrous layer.

small intraluminal thrombus, all were excellent. The crimped nature of the graft persisted to a certain extent after many months but the lining membrane remained thin, glistening, and smooth (Fig. 6). Microscopically the strands of the yarn were well incorporated between the thin, smoothly lined inner fibrocellular layer and an outer fibrous coat. As the new aorta is built about the crimped plastic material the ridging is diminished by the laying down of alternately thin and thicker fibrocellular layers inside and outside the graft (Fig. 7). Fibroblasts invade the interstices between the plastic filaments and firmly unite the graft to the inner and outer coats. The lining membrane is covered with flat endothelial-like cells.

The gross and microscopic appearance of grafts made of polythene fused by heat between 2 thin layers of nylon and of a single layer of the same polythene and nylon fused by impulse sealing, as well as the Vinyon N grafts, has been previously described. Of these 3 types of grafts, those made by heat fusion of polythene between 2 layers of nylon were better than the other 2, but inferior to grafts made of nylon filter fabric and the braided nylon tubular grafts.

The pig heterografts were quite unsatisfactory. They tended to undergo aneurysmal dilatation and to develop intramural thrombi (Fig. 8). The cow heterografts were a little better but were also generally unsatisfactory. One ruptured after 42 days of implantation. Of the older grafts, though one was considered excellent (Fig. 9, *B*) and one good, the majority showed degenerative changes and considerable dilatation (Fig. 9, *A*). Microscopically (Fig. 10) these grafts showed a new fibrocellular layer on the interior, sometimes smooth, sometimes covered with adherrent thrombi. On the external surface a thin, loose fibrous layer was present. The graft itself showed extensive degeneration and appeared chiefly as amorphous acellular material. Only a few viable fibroblasts could be identified.

## DISCUSSION

Throughout these experiments it was evident that no plastic graft was quite as easily sutured to the ends of the aorta as the homograft. Nevertheless, there was no real difficulty in fixing the ends of the plastic graft to the host aorta. Of the various plastic grafts subjected to study, those made of washed nylon filter fabric and the braided nylon tubular grafts of Edwards and Tapp[7] proved superior to the others. These 2 types of grafts were indeed somewhat superior to the homografts, principally because after fairly long periods of observation the lining membrane tended to remain smooth and they showed no evidence of degenerative changes or calcification, alterations which were observed in some of the older homografts. Whether much longer periods of observation would demonstrate such alterations in these plastic grafts is not known. The experiments of Creech and his associates[3, 4] with experimental hypercholesterolemia suggest that new aortas built about plastic prostheses are far less likely than homografts to undergo athrosclerotic-like changes.

Hufnagel and his colleagues[9, 10] reported rather satisfactory results from implantation of freeze-dried heterografts, as did Kimoto[11] with alcohol-preserved

heterografts. Creech and his associates, on the other hand, obtained poor results with freeze-dried heterografts. Our brief initial experiences with alcohol-preserved pig and cow heterografts implanted into aortic defects of dogs gave disappointing results.

In other clinical studies we have found prostheses made of nylon filter cloth to be most satisfactory for aortic and aortic bifurcation grafts. Our experiences with the Edwards-Tapp crimped braided nylon tubular grafts for end-to-side by-pass grafting procedures have also been good.

## CONCLUSIONS

From our experimental observations we conclude that grafts of small diameter made either of nylon filter fabric or of braided nylon treated with formic acid and silicone are very satisfactory as canine aortic prostheses. Relatively long-term observations suggest they may be superior to freeze-dried homografts.

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# ACUTE LIGATION OF THE PORTAL VEIN

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ACUTE ligation of the portal vein is of recurring interest. Historically, Oré in 1856,[26] during an investigation into the formation of bile, first recorded the fact that sudden obliteration of the portal vein resulted in the death of 3 dogs within an hour. Claude Bernard,[2] in 1859, and Schiff,[29] in 1861, independently found the same result. Initially Bernard postulated the cause of death as something other than solely a bloody congestion of the intestines, but later (1877)[1] he wrote "The mechanism of death is easy to understand. All the blood tends to accumulate in the vessels of the intestine. The brain and other organs become exsanguinated and the animal dies, in fact, of anemia." Schiff,[29] by tying the portal vein of a cat, claimed to suppress biliary secretion, and he considered that death was due to a toxic substance in the portal blood which the liver destroyed to form the elements of bile. These two opposing theories, the one that death is due simply to exsanguination, the other that some toxic material is produced, thus appeared early and have continued to have their adherents to the present time.

Schiff's theory appeared to receive support from the work of Tappeiner.[31] In the rabbit he estimated that 16.2 per cent of the blood was trapped in the intestines after the portal vein had been ligated, but probably little weight can be attached to his figures, for he estimated the total blood volume to be only 4.68 per cent of its body weight and that blood amounting to 3.08 per cent of its body weight could be removed without death occurring. Nevertheless, this paper was much quoted, and, in 1877, Lautenbach[19] of Philadelphia thought he had disposed of anemia as the cause of death because he maintained that (1) the arterial blood pressure rises immediately following ligation, (2) the animals never show convulsions prior to death, and (3) ligature of the hepatic veins, which produces an analogous stasis, is not followed by the same symptoms. He maintained that an unknown poison caused death and to prove this thesis, injected 3 ml. of blood from the ligated portal vein of dogs into frogs. All died in 3 hours, in a fashion similar to the dogs which had their portal veins ligated.

This work was quickly refuted by Mosselman and Liénaux[23] in 1885, who, in a careful series of experiments with dogs after ligation of the portal vein (1) injected the portal vein blood into frogs without results, (2) could maintain the dog alive longer, and restore its pressure with blood transfusion, (3) could prolong life by ligating the feeding arteries, (4) could allow survival by releasing the ligature, and (5) showed that complete ligation of the hepatic veins

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only was extremely hard to perform. Accordingly, they maintained that death was indeed due to diminution of the quantity of circulating blood, and to an insufficiency of its oxygen or carbon dioxide content. Their work received support from Castaigne and Bender,[7] in 1899, who also showed that life was prolonged by transfusion and by ligation, in this case, of the aorta above the celiac axis. Castaigne and Bender also quote Netter,[24] in 1884, as originating the suggestion that toxins are produced in the bowel and these, unable to be detoxified by the liver, cause death.

Oré's paper[26] recorded the fact that dogs survived chronic obliteration of the portal vein. Examination of his dogs showed that an anastomosis between the great mesenteric vein and the inferior vena cava had developed. Claude Bernard[2] recorded a similar experiment, and, in 1874, Solowieff[30] first demonstrated that dogs could survive occlusion of the portal vein if the branches were ligated at different times. Neuhoff[25] repeated Solowieff's experiments and confirmed them. He found, as had the previous authors, that a well-marked "hepatopetal"[27] collateral circulation developed. He was the first to contemplate ligation of the portal vein as a surgical procedure to prevent the spread of pylephlebitis, but did not actually perform the operation.

Until 1932, no other effort than Tappeiner's seems to have been made to measure the amount of blood trapped within the gastrointestinal tract. This is obviously the crux of the matter. If death is due only to exsanguination into the bowel, it should be possible to produce death in a comparable time and manner by bleeding from a normal dog a volume of blood equal in amount to that trapped in the gastrointestinal tract. In 1932, Elman and Cole[10] made an attempt to measure this amount of blood. They weighed the eviscerated intra-abdominal gastrointestinal tract, including the spleen and pancreas, following ligation of the portal vein and compared this weight with the weight of eviscerated organs of normal dogs of similar weight and sex in whom the portal vein had not been tied. The increase in weight of the organs of the dog with a ligated portal vein was assumed to be due to the passage of blood into the splanchnic vascular bed. In 4 dogs this increase was found to be 5.2 per cent of the body weight, a weight of blood which, they felt, was sufficient to reduce the blood pressure below that compatible with life. In 1933, McMichael and Smirk,[20] working with rats, recorded as an incidental observation that in 2 rats with complete obliteration of the portal vein, the weight of the gut increased from an average of 5.5 per cent of the body weight to 11.5 per cent and 12.5 per cent. Both these rats died in a few hours. But in 1935, Boyce, Lampert, and McFetridge[5] repeated the experiments of Elman and Cole using 7 dogs. Their figure for the increase in weight of the gut was 3.05 per cent of the body weight. Naturally their conclusions differed, for they were able to bleed a control series of dogs 4 to 5 per cent of their body weight without death. Beyond 5.8 per cent the animals died of shock. Their theory was that death following ligation of the portal vein was due to neurogenic shock, which produced the rapid initial fall in blood pressure, and the fall was maintained by the loss of blood. Despite these discrepant findings, probably the result of using small numbers of animals

in rather crude experiments, little further was done until 1950, when Mallet-Guy, Devic, and Gangolphe[21] repeated Elman and Cole's work. They found that blood amounting to 5.0 per cent of the body weight was trapped within the gastrointestinal tract. By using Chicago-blue dye they also measured the preligation and postligation circulating blood volumes and found a decrease of 4.9 per cent of the body weight, or 49.3 per cent of the circulating blood volume.

Most of the experiments quoted above were performed with the dog, although some workers used the rabbit and others, the rat. In these animals, death inevitably follows sudden occlusion of the portal vein. Claude Bernard[2] ligated the portal vein of a pigeon. The bird survived ligation but died next morning from an unknown cause. His work was repeated, using turkeys, by Bolognesi.[4] Neither death nor disturbance to the bird occurred. Birds have a large communication in the pelvis between portal and systemic veins (the venous system of Jacobson), and blood from the viscera can flow indifferently into the vena cava or into the portal vein and thence to the liver. Only in mammals does the portal vein form a closed system communicating with the systemic circulation only through the liver.

In 1949, Milnes and Child[22] showed that sudden, complete occlusion of the portal vein in *Macacus rhesus* monkeys was not fatal. Portal venography showed that pelvic portosystemic anastomoses occurred naturally, and immediately carried much of the blood. Observers had noted early that unless the ligature was placed on the hepatic side of the last portal vein tributary, survival could occur.[7, 9, 17] Both Oré[26] and Claude Bernard[1] had noted that peritoneal adhesions carried portal systemic anastomoses and that the portal vein could be ligated in animals with such adhesions. Brunschwig[6] had no success when attempting this, however, as an experimental method to enable dogs to survive acute ligation. It would appear that when there is adequate collateral circulation, either by naturally occurring portosystemic venous communication, by adhesions, or by malposition of the ligature, survival occurs after portal vein ligation. Naturally occurring portosystemic anastomoses are limited, in general, to those animals who have a portion of their intestinal tract and associated organs placed retroperitoneal.

In the dog, whose viscera swing free on a long mesentery, preliminary dissections of the injected portal system showed the anastomotic veins accompanying the vagi at the cardia to be the only important connections between the portal and systemic veins. Only infrequent slender venules connect the mesentery with the lumbar veins and the lower rectum with the prostatic veins.

The review of the literature shows that an accurate estimation of the amount of blood trapped in the splanchnic circulation of the dog after portal vein ligation has not been made. This information is essential to establish the part of oligemia in the invariably fatal outcome. If the degree of oligemia by itself is insufficient to account for the inevitability and rapidity of death, then other factors must be considered. It is the purpose of this paper to describe a method of measuring the decrease in circulating blood volume following portal vein ligation.

## METHOD

Pound dogs were used and were starved overnight, but water restrictions were not enforced. Anesthesia was induced by intravenous sodium pentobarbital (30 mg. per kilogram body weight). The dogs were intubated with an endotracheal tube and placed on a warmed operating table. The abdomen was opened by a midline incision. Blood loss did not exceed 10 to 20 ml. During the period between manipulations, the abdominal wall was closed by Allis tissue forceps; if this was impossible, the wound was protected by towels soaked in saline. The instant of death was taken as the last contraction of the left ventricle of the heart. This point was usually preceded by several convulsive respiratory movements.

Under the standard conditions described, the portal vein was identified and was cleared upward to the bifurcation, a black silk ligature was applied on the hepatic side of the last tributary, and the ends were brought out through the abdominal wound. This dissection usually caused fluctuations of the blood pressure, and time was allowed for this to return to normal. When the pressure finally settled, the ligature was tied in such a way that the viscera was disturbed as little as possible. The arterial blood pressure was obtained by a mercury manometer connected to the carotid artery. The portal venous pressure was obtained by cannulating a splenic vein in the gastrosplenic ligament. The pressure was recorded by means of a transducer, amplifier, and direct-writing oscillograph.

The blood volume determinations were made using Reeve and Veall's[28] modification of the procedure of Hevesy and Zerahn.[14] Ten milliliters of venous blood were withdrawn from a forepaw vein of the dog into a 10 ml. syringe containing heparin. Eight milliliters of this blood were incubated with 40 microcuries of carrier-free $P_{32}$ of high specific activity for approximately 1½ hours in a 10 ml. centrifuge tube rotated in a water bath at a constant temperature of 37° C. The cells were then separated from the plasma by centrifuging and resuspended in saline. The separation and resuspension was done three times.

Two milliliters of the freshly prepared suspension of labelled red cells were injected into a femoral vein. After allowing 5 minutes for mixing to occur, 10 ml. of blood were withdrawn from the contralateral femoral artery and placed in a small glass beaker containing sodium citrate crystals as an anticoagulant and powdered saponin to produce lysis of the red cells. Five 1 ml. samples of this blood were counted separately for activity, using a glass Veall re-entrant type liquid beta Geiger counter. All blood samples were obtained using dry siliconed all-glass syringes.

The activity of the specimen of blood withdrawn from the femoral artery was compared with the activity of the original 2 ml. suspension of labelled red cells. The activity of this was obtained by using the same 2 ml. syringe to draw up the suspension diluting it to approximately the same volume as the blood volume of the dog by injecting it into a Winchester bottle containing 2,000 ml. of water and again counting 5 samples, each of 1 ml. of this dilution, for activity. If the total activity of the injected $P_{32}$ labelled red cells is A

counts per second and the activity of 1 ml. of the blood withdrawn from the animal is B counts per second, then the blood volume, V, is given by the formula $BV = A$, or $V = \frac{A}{B}$.

When a second blood volume determination was required, 10 ml. of blood were withdrawn from the ipsilateral femoral artery and counted for background activity. Immediately following the withdrawal, an additional 2 ml. of $P_{32}$ labelled red cells were injected into the femoral vein not previously used, and again, after 5 minutes, 10 ml. of blood were obtained from the femoral artery not previously used.

In order to discover whether adequate time was allowed for mixing of the injected red cells with the circulating red cells, 2 types of experiments were carried out.

*Serial Estimation of the Activity.*—A 2-way stopcock attached to a needle was inserted into the left femoral artery. Two ml. of $P_{32}$ activated red cells were injected into the right femoral vein. At 2-minute intervals thereafter, 2 ml. samples of blood were obtained from the femoral artery. Before each sample was collected, 1 ml. was allowed to flow through the needle and stopcock to flush out the blood remaining from the previous sample.

*Continuous Record of Activity.*—The femoral vessels on both sides were exposed. On one side the femoral artery was divided, cannulated with size 16 polyethylene tubing filled with heparinized saline and arranged so that a helix was formed through which the blood flowed. The helix was placed between 2 self-quenching, thin, end-window Geiger-Mueller counters, wired in parallel. Two milliliters of $P_{32}$ labelled red cells were injected into the contralateral femoral vein. By means of a rate meter arranged to record through a graphic ammeter recorder, a continuous record of the level of activity of the circulating blood could be obtained.

## RESULTS

*Acute Ligation of the Portal Vein.—*

*Length of survival following acute ligation:* Table I shows the survival time following acute ligation under 3 different circumstances: (1) acute ligation of the portal vein only, (2) acute ligation of the portal vein, together with ligation of the esophageal anastomotic veins, and (3) acute ligation of the portal vein with the dogs being given heparin.

Acute ligation in 14 dogs caused death in an average of 79.7 (±18.9) minutes, a figure which is in accord with that recorded in the literature. When, in addition, a ligature was placed around the intra-abdominal esophagus in 11 dogs, the time of survival was shortened to 56.0 (±8.5) minutes. In 9 dogs with acute ligation of the portal vein without esophageal ligature, but given heparin (10 mg. per kilogram), time of survival was 88.6 (±22.9) minutes. There was a significant difference ($p < 0.01$) between the length of survival with or without esophageal ligatures, but no significant difference between survival with or without heparin.

*Blood pressure:* Immediately following ligation of the portal vein the arterial pressure dropped rapidly in the first few minutes and then more slowly

TABLE I. SURVIVAL TIMES (MINUTES) AFTER OCCLUSION OF PORTAL VEIN

| DOG NO. | ESOPHAGEAL VESSELS OCCLUDED | DOG NO. | NO ESOPHAGEAL LIGATURE | DOG NO. | NO ESOPHAGEAL LIGATURE HEPARIN— 10 MG./KG. |
|---|---|---|---|---|---|
| 1 | 75 | 12 | 50 | 26 | 124 |
| 2 | 59 | 13 | 70 | 27 | 90 |
| 3 | 46 | 14 | 56 | 28 | 93 |
| 4 | 54 | 15 | 85 | 29 | 61 |
| 5 | 53 | 16 | 95 | 30 | 110 |
| 6 | 52 | 17 | 89 | 31 | 55 |
| 7 | 58 | 18 | 95 | 32 | 67 |
| 8 | 61 | 19 | 77 | 33 | 102 |
| 9 | 48 | 20 | 47 | 34 | 95 |
| 10 | 63 | 21 | 74 | | |
| 11 | 47 | 22 | 95 | | |
| | | 23 | 85 | | |
| | | 24 | 85 | | |
| | | 25 | 113 | | |
| Average with calculated standard deviation | 56.0 ± 8.5 | | 79.7 ± 18.9 | | 88.6 ± 22.9 |

to reach a plateau at 30 to 40 mm. Hg after about 10 to 20 minutes. It stayed at this level with only minor fluctuations until just prior to death, when there occurred a more sudden fall to zero pressure.

When simultaneous records were taken of the portal venous pressure and arterial pressure, it was shown that the portal venous pressure rose from a preligation level of around 7 mm. Hg to a maximum of 50 to 60 mm. Hg in about 2 minutes; thereafter the portal venous pressure declined to a level midway between the diastolic and systolic systemic arterial pressures and thereafter paralleled the fall in these pressures. A typical result is shown in Fig. 1.

Following ligation, blood is continuously supplied to the splanchnic vessels, from which it cannot escape. As the circulating blood volume is rapidly reduced, so the systemic blood pressure will fall, until it is equal to the level to which the

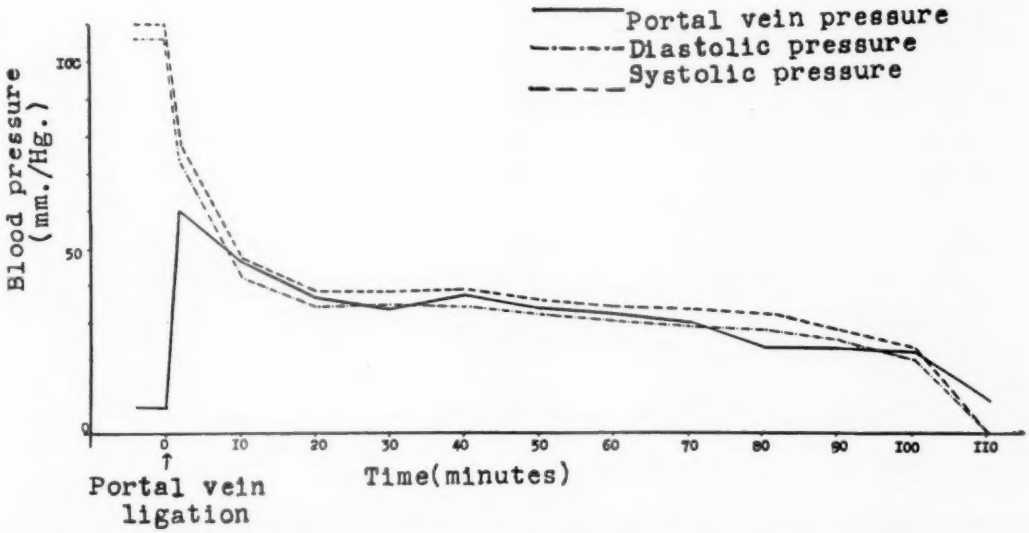


Fig. 1.—Concurrent recordings of portal vein blood pressure and systemic blood pressure.

portal venous pressure rises. While the pressures remain equal during the period of the plateau, the only blood entering the splanchnic vascular bed will be to replace the blood escaping from the bed by the portosystemic anastomoses and the blood lost by hemorrhage into the bowel wall. The splanchnic bed is to all intents excluded from the circulation. If the portosystemic anastomoses are occluded, the exclusion is more complete. Therefore, a measurement of the blood volume during this period will measure only the circulating systemic portion.

*Blood Volume Estimations.—*

The results of 11 experiments are summarized in Table II. The average circulating blood volume was 76.9 (±6.56) ml. per kilogram body weight. Thirty minutes after occlusion of the portal vein and 10 minutes after ligation of the esophagus and its vessels, the average systemic circulating volume was 32.7 (±8.23) ml. per kilogram, a reduction of 44.2 ml. per kilogram or 57.9 per cent (±8.77) of the original blood volume.

TABLE II. REDUCTION IN CIRCULATING BLOOD VOLUME

| DOG | SEX | WEIGHT (KILOGRAM) | PRELIGATION CIRCULATING BLOOD VOLUME (MILLILITER) | PRELIGATION CIRCULATING BLOOD VOLUME (MILLILITER PER KILOGRAM) | POSTLIGATION CIRCULATING BLOOD VOLUME (MILLILITER) | POSTLIGATION CIRCULATING BLOOD VOLUME (MILLILITER PER KILOGRAM) | REDUCTION OF CIRCULATING BLOOD VOLUME (PER CENT) |
|---|---|---|---|---|---|---|---|
| 1 | F | 9.1 | 798 | 87.7 | 399 | 43.8 | 50.0 |
| 2 | M | 18.2 | 1452 | 79.8 | 826 | 45.4 | 43.1 |
| 3 | F | 4.5 | 347 | 77.1 | 113 | 25.1 | 67.4 |
| 4 | M | 10.0 | 797 | 79.7 | 356 | 35.6 | 55.3 |
| 5 | M | 14.1 | 1023 | 72.6 | 468 | 33.2 | 54.3 |
| 6 | M | 10.0 | 675 | 67.5 | 181 | 18.1 | 73.2 |
| 7 | F | 15.1 | 1186 | 78.5 | 583 | 38.6 | 50.8 |
| 8 | M | 15.9 | 1067 | 67.1 | 424 | 26.7 | 60.3 |
| 9 | M | 17.3 | 1435 | 82.9 | 570 | 33.0 | 60.3 |
| 10 | M | 25.9 | 1930 | 74.5 | 914 | 35.3 | 52.6 |
| 11 | F | 10.0 | 788 | 78.8 | 244 | 24.4 | 69.0 |
| Average with calculated standard deviation | | 13.6 | 1045 | 76.9 ± 6.56 | 462 | 32.7 ± 8.23 | 57.9 ± 8.77 |

Following ligation of the portal vein, the average counting rate of the systemic blood fell to 83.0 per cent (±15.2) of the preligation value, while the portal venous count rose to 117.2 per cent (±15.9) of its original value. Five minutes after the second injection of labelled red cells, the average counting rate of the portal venous blood rose only 1.2 per cent (±6.9) above the background count for the blood immediately prior to the second injection, whereas the average systemic count rose 184.2 per cent (±55.3).

In a preliminary series of 7 dogs, a similar type of experiment was undertaken except that the portal vein only was ligated and collateral vessels were ignored. After the second injection of $P_{32}$ labelled red cells, a rise in the average portal venous blood counting rate of 17.8 per cent (±22.2) was noted, when the average systemic blood counting rate rose 175.6 per cent (±53.0). This indicated the degree of leakage of labelled red cells into the splanchnic vascular bed, when these main anastomotic channels were not occluded. It is

also further confirmation that in the dog, the main portosystemic venous anastomoses occur at the lower end of the esophagus connecting the gastric portal vein to the esophageal systemic veins.

## DISCUSSION

It is possible to carry out accurate determinations of circulating blood volumes using the $P_{32}$ labelled red cell method. By using the Veall counter, it is not necessary to estimate the hematocrit to calculate blood volume, for the activity of whole blood is counted and it is unnecessary to apply any correction factor for plasma trapped within the red blood cells.[28] Fig. 2 shows the mixing curves in 2 experiments after the injection of 2 ml. of $P_{32}$ labelled red cells; corrected counts of activity were obtained by 2 ml. samples of blood withdrawn at the times shown. Mixing is complete in 5 minutes, though the activity of the injected cells does not remain constant but shows a persistent steady decline, as has been found by other investigators.[13, 18, 28]

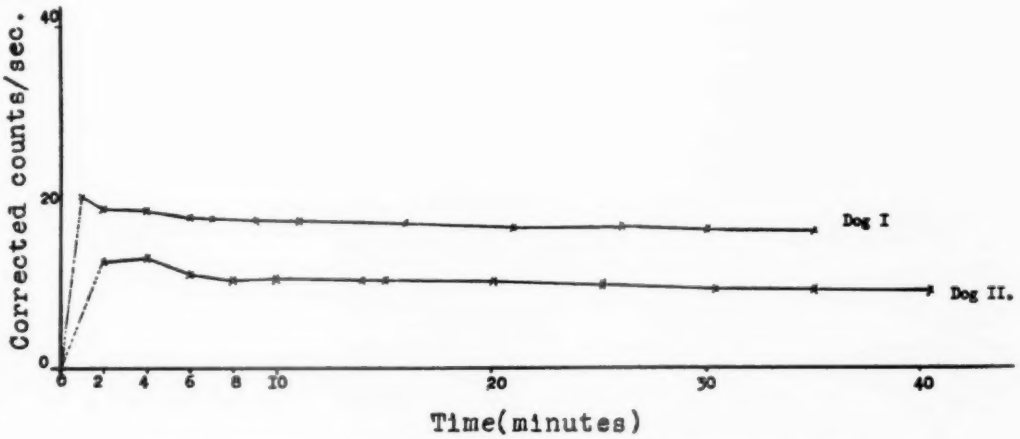


Fig. 2.—Mixing of $P_{32}$ labelled red cells in the general circulation.

Fig. 3 shows similar results using the method of continuous records of the counting rate employing the end-window Geiger counters. Again mixing is shown to be barely complete in 5 minutes.

Following ligation of the portal vein with the sequestration of blood within the portal vascular bed, mixing of injected labelled red cells with the systemic circulating blood is slowed due to the reduced cardiac output. Fig. 4 shows the rate of mixing occurring in the systemic circulation at intervals for 20 minutes after injection of $P_{32}$ labelled red cells in two experiments. The red cells were injected 20 minutes after the portal and esophageal anastomotic veins were ligated. Again, mixing is barely complete after 5 minutes, but the counting rate starts to fall by the tenth minute. It is during this short period that it is necessary to withdraw the blood to avoid the error—on the one hand, of incomplete mixing; on the other, of the decline in the counting rate resulting from both the sequestration within the splanchnic vascular bed and the normally occurring decrease in counting rate.

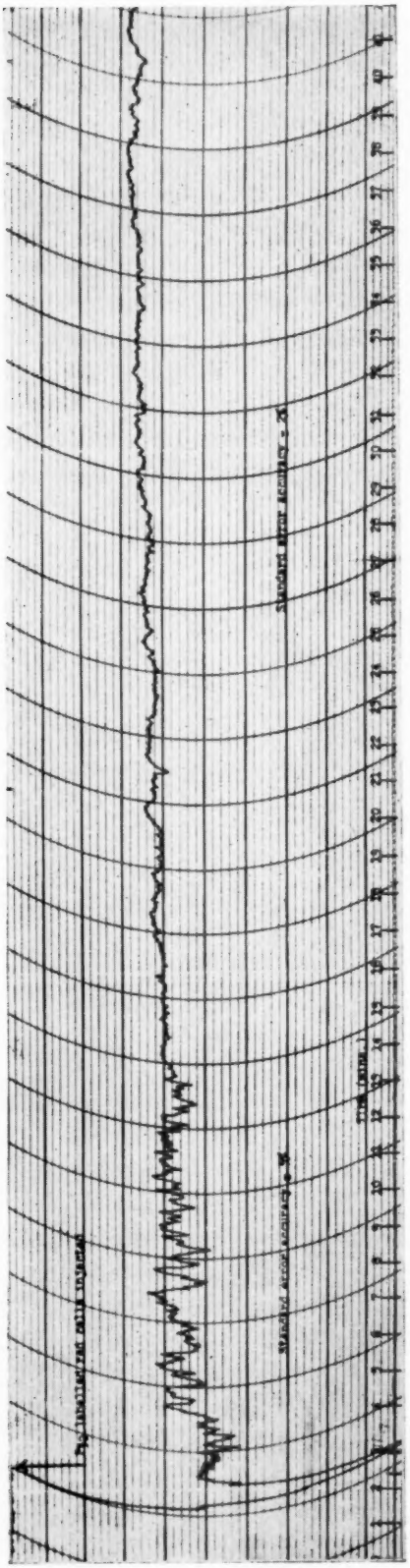

Fig. 3.—Mixing of $P_{32}$ labelled red cells in the general circulation. Continuous record of counting rates. Full scale meter range = 5,000 counts per minute.

The injection of $P_{32}$ labelled red cells for the second blood volume determination was made into the inferior vena cava, and the systemic sample was taken from the femoral artery in order to attempt to reduce the effect of sluggish peripheral flow. The error introduced by incomplete mixing will be such that dilution will not be completed, and thus too low a value for the circulating blood volume will be obtained. As the error is likely to be greater in the second blood volume estimation than in the first, the values obtained for the decrease in circulating blood volume are likely to be too great.

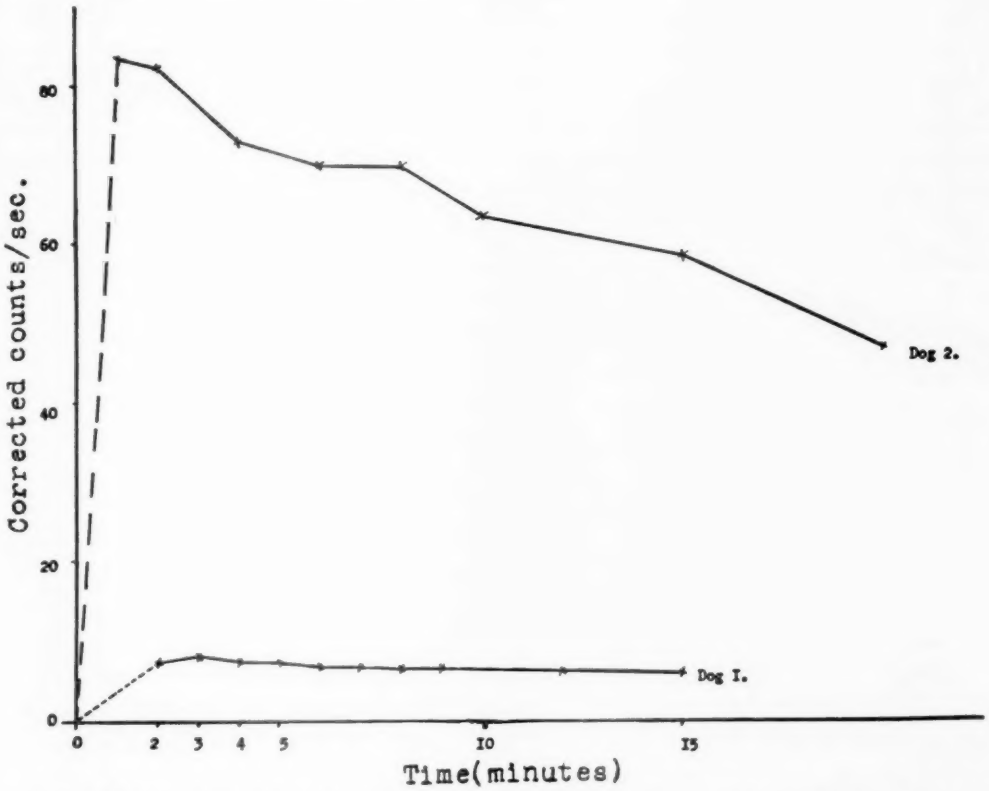


Fig. 4.—Mixing of $P_{32}$ labelled red cells in general circulation. Thirty minutes after portal vein ligation.

Escape of red cells into the sequestrated circulation has been seen to be slight, and the error introduced by this is probably relatively less but will give apparently too great a dilution and thus too low a value for the decrease in circulating blood volume. The estimation of the circulating blood volume was made 30 minutes after the occlusion of the portal vein during the period of the blood pressure plateau and about midway in the time of survival. Though blood continued to be lost into the bowel, this was to some extent offset by the return of blood from the splanchnic bed as the arterial pressure declined prior to death and possibly by plasma returned from the bowel by the lymphatics.

In order to discover whether consecutive estimations of blood volume could be made using the $P_{32}$ method, 2 experiments were carried out, and the results are found in Table III. In the first experiment, the second determination

followed immediately after the first, and the third 30 minutes after the second. The differences were 3.1 per cent and 2.2 per cent, respectively. In the second experiment, the second determination followed immediately after the first and the difference was 3.1 per cent.

TABLE III. CONSECUTIVE ESTIMATIONS OF BLOOD VOLUME

| DOG NO. | SEX | WT. (KG.) | FIRST BLOOD VOLUME DETERMINATION (ML.) | SECOND BLOOD VOLUME DETERMINATION (ML.) | THIRD BLOOD VOLUME DETERMINATION (ML.) |
|---|---|---|---|---|---|
| 1 | M | 18.8 | 1338.0 | 1380.0 | 1412.3 |
| 2 | F | 6.8 | 466.0 | 452.3 | |

These experiments have shown that the reduction in circulating blood volume following sudden and acute ligation of the portal vein is 57.9 per cent of the original volume, or 44.2 ml. per kilogram body weight. This value cannot be compared with those obtained by Elman and Cole[10] or Boyce.[5] Their values reflected only the quantity of blood introduced into the splanchnic vascular bed and ignored that portion normally contained within the vessels of the bed.

Recent investigations[16] have indicated that the blood volume contained within the splanchnic circulation of dogs under conditions similar to the present experiments is 17.7 ml. per kilogram body weight. If this quantity of blood is subtracted from the circulating blood volume taken as 76.9 ml. per kilogram body weight, the systemic circulation contains 59.2 ml. per kilogram body weight. After ligation of the portal vein, the systemic circulating blood volume is reduced to 32.7 ml. per kilogram body weight. The true reduction in the circulating blood volume is, therefore, the difference between this figure and the value for the circulating blood volume with the splanchnic bed excluded (59.2 ml. per kilogram), that is, 26.4 ml. per kilogram body weight or 44.6 per cent for the remaining circulating blood volume is required to fill a vascular bed reduced by the normal capacity of the splanchnic bed. It is this figure which corresponds to that of Elman and Cole.

An experiment similar in design to the one described in this paper was performed by Mallet-Guy, Devic, and Gangolphe.[21] Unfortunately they chose the dye method to estimate the blood volume. This meant that 48 hours had to elapse between the first and second blood volume estimations to allow the dye of the first estimation to disappear. They also ignored portosystemic anastomoses. The value they obtained of a reduction in circulating blood volume of 49.3 per cent is not comparable to that of Elman and Cole or Boyce, for it, too, includes the blood normally present in the splanchnic vascular bed. The comparable figure is 36.7 per cent.

Efforts to determine the volume of blood which is required to be bled to produce fatal levels of shock have been abandoned, for the response of the dogs is so variable that no figure is useful. Of much more value are the figures obtained by bleeding to arbitrary levels of irreversible shock. The method employed by Fine and his group[11] is most comparable to the present experiments. The dog is bled rapidly into a container until its pressure falls to 30 mm. Hg. The average loss is 53 ml. per kilogram in 30 to 45 minutes. This level of blood

pressure then remains steady until death which occurs, on the average, 5.3 hours later. In the present experiments this container is analogous to the splanchnic circulation, for with a rise in systemic pressure, the splanchnic circulation takes up blood and with a fall, it gives up blood. By his methods, his animals survive many hours longer than they do following ligation of the portal vein, even though on the average, the level of the blood pressure is lower and the amount of blood removed is greater. His preparations differ in that the anesthetic used is morphine supplemented by local anesthetic, whereas in the present experiments, sodium pentobarbital is employed. The present series of animals were also subjected to the trauma of opening the abdomen and handling the viscera.

The effect of pentobarbital anesthesia on the survival of dogs subjected to various methods of producing hemorrhagic shock has been the subject of investigation. In these experiments the usual dose to produce surgical anesthesia has been used. This is probably not a factor in the length of survival. Using different anesthetic agents, previous workers[5, 10] had substantially the same survival times following ligation of the portal vein.

Ingraham[15] stated that pentobarbital anesthesia in two-thirds of the dose normally used (21.4 mg. per kilogram body weight) has no effect on the course of events in hemorrhagic shock. Wang[32] found there was no significant change in the final bleeding volume after pentobarbital anesthesia. It does, nevertheless, cause enlargement of the spleen, produce hemodilution, and cause congestion of the viscera.[3, 8, 12, 33]

In order to see whether splenectomy would have any effect on the course of events after ligation of the portal vein, 4 experiments were done. In 2, the abdomen was opened, the portal vein was cleared, and a ligature was placed in the usual manner. The splenic artery was ligated; when the spleen had shrunk, the splenic pedicle was clamped; and the spleen was excluded from the circulation. The portal vein was then ligated and the dogs died in 56 minutes and 72 minutes, respectively, with no change in the course or in the post-mortem appearance of the intestines. The blood pressure fell, after ligation, to a level of between 80 and 90 mm. Hg over 10 minutes and then declined slowly until a pressure of 30 to 40 mm. Hg was reached. In the third and fourth experiments, the decrease in circulating blood volume was measured after portal vein ligation but with the spleen removed (Table IV). Both of these dogs showed a greater degree of extravasation of blood into the mesentery than those without splenectomy. However, their course was uninfluenced, and the decrease in circulating blood volume was within the range of those dogs without splenectomy. In effect, the splanchnic vascular bed seems to have a huge capacity for distention, and this is not diminished notably by splenectomy. The capacity of the spleen in dogs has not been recorded.

This indicates that whatever the effect of sodium pentobarbital is on the spleen, it has little influence on the course of events of these experiments, for there can be no greater stimulus to splenic enlargement than a rise in portal venous pressure nor decrease in the splenic volume than total removal.

TABLE IV. REDUCTION IN CIRCULATING BLOOD VOLUME FOLLOWING SPLENECTOMY AND PORTAL VEIN LIGATION

| DOG | SEX | WEIGHT (KILOGRAM) | BLOOD VOLUME (MILLILITER) | BLOOD VOLUME (MILLILITER PER KILOGRAM) | BLOOD VOLUME FOLLOWING SPLENECTOMY AND PORTAL VEIN LIGATION (MILLILITER) | PER CENT REDUCTION | SURVIVAL TIME (MINUTES) |
|---|---|---|---|---|---|---|---|
| 1 | M | 20.9 | 1893 | 90.5 | 754.7 | 60.1 | 68 |
| 2 | M | 14.1 | 874 | 62.0 | 471.0 | 46.1 | 72 |

In conclusion, it is suggested by these experiments that death following acute ligation of the portal vein cannot be attributed solely to decrease in circulatory blood volume. What other factors are involved is not known. Certainly the most important factor is the reduction in the circulating blood volume. Those investigators who have pointed out the fact that measures which prevent the loss of blood into the splanchnic circulation, such as removal of the gut or ligation of the mesenteric arteries, or which replace the blood loss, either by transfusion of blood or of other fluid and thereby increase survival time, have failed, however, to explain the reason for the inevitability of death and the decreased length of survival, which is not paralleled by bleeding the same amount of blood from a normal dog.

## SUMMARY

1. The literature pertaining to acute ligation of the portal vein has been reviewed.

2. Following acute ligation of the portal vein in dogs, the average survival time is 79.7 minutes. With occlusion of the major portosystemic anastomotic channels, the average survival time falls to 56.0 minutes. If ligation is incomplete, the dog may survive.

3. The arterial pressure falls within 10 to 20 minutes to a level of 30 to 40 mm. Hg at which level it remains until just prior to death.

4. Thirty minutes following acute ligation the circulating blood volume decreases by 57.9 per cent of the original blood volume, or by 44.6 per cent of the blood volume circulating exclusive of the splanchnic bed.

5. Splenectomy does not affect the outcome.

6. It is concluded that death cannot be attributed solely to a decrease in the circulating blood volume.

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# EXPERIMENTAL AND CLINICAL ADVENTURES WITH LARGE DOSES OF GAMMA AND OTHER GLOBULINS AS ANTICANCER AGENTS

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## INTRODUCTION

CLINICAL evidence of host resistance to malignancy is not difficult to find. The literature has many isolated articles reporting unusual instances in which a malignant tumor has "spontaneously regressed." Unfortunately, only a few of these can be accepted after the following criteria have been met: (1) biopsy of the primary tumor; (2) no therapy or a demonstrated lack of effectiveness of therapy with objective evidence of continuing growth confirmed by biopsy; and (3) disappearance of the tumor mass confirmed by appropriate biopsy.

Although it would be difficult to ignore the role of host immunity, other explanations are possible: such as, (1) hormonal imbalance resulting in a therapeutic effect; (2) intercurrent infection with release of bacterial toxins or other substances inimical to tumor cell growth; (3) Hyperpyrexia with selective death of temperature susceptible cancer cells; (4) delayed death of the tumor subsequent to changes in its blood supply following partial excision or irradiation; (5) exhaustion of growth factors essential for continued viability of tumor cells; (6) mutation to a more rapidly growing cell type sensitive to one of the hypothetical defenses above; and (7) inflammation leading to fibrosis and a diminution in blood supply.

Of equal interest are reported cases in which patients have remained for months or years apparently free of all evidences of malignancy following excision of the primary tumor only to show sudden evidence of widespread involvement.

Classical examples of spontaneous regression are most frequent with malignant melanoma (particularly of the eye), breast cancer, and hypernephroma.[10, 21] Sporadic case reports of the regression of other sorts of tumors can be found in the literature,[6] but such observations are surprisingly few. No presently known metabolic or hormonal deficiencies could explain the apparent regression or prolonged quiescence in such diverse kinds of tumors. The development of an immune state could account for tumor regression regardless of the type of tumor.

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## CLINICAL STUDIES

The concept of immunity to cancer is an old one and well verified experimentally with transplanted tumors. No practicable experimental approach has been possible for the production of either an active or a passive immunity in humans with spontaneous tumors. The development of an active immunity could probably be successful only if the course of the disease were arrested by some other means, in the same way that the prophylactic development of an active immunity to diphtheria is impractical once the disease has become established. The transference of passive immunity has also not been practicable because of the intensity of the reaction likely to follow the injection of large amounts of heterologous serum and the difficulty of obtaining large amounts of human "immune" serum.

If some degree of natural immunity to cancer exists, it appears most probable that any circulating antibody would be found in the globulin fraction. Large quantities of human gamma globulin have only recently been made available commercially when the processing of serum to gamma globulin in an attempt to treat poliomyelitis was begun following indications that a state of temporary passive immunity to this disease could be attained.

Since such material had been available, it appeared logical on two counts to attempt the treatment of patients with various types of cancer with massive doses of "nonspecific" human gamma globulin, which could provide passive immunity to cancer if it contained natural antibodies. Further, if one theorized that the control of serum protein production is through the concentration of serum proteins in the blood, such a control would be lacking in multiple myeloma and uninterrupted production of the abnormal proteins would continue unchecked. The addition of large quantities of normal globulin might serve to support the normal controlling mechanism and check the production of endogenous abnormal globulins. Multiple myeloma might therefore be expected to respond to gamma globulin therapy for two reasons.

The effectiveness of gamma globulins has been well demonstrated in certain infections, especially measles. A condition of agammaglobulinemia has been described,[3] its effects on immunity to a number of antigens, bacterial and tissue investigated, and the therapeutic use of gamma globulin has been studied.[7, 13, 17] Currently, the relationship between gamma globulin production and antibody level is being studied intensively by many groups.

Only relatively small amounts of gamma globulin have previously been given intravenously and severe reactions have occurred. For our purpose, intravenous administration was the only feasible route. Each patient was given small initial doses of not more than 5 Gm. of commercial human gamma globulin in 500 c.c. of 5 per cent glucose. On successive days, increasingly large amounts were given to a maximum of 100 Gm. In most instances, the daily infusion was limited to 50 Gm.* (See Table I and Figs. 1 to 3).

Both isotonic saline and 5 per cent glucose were used as vehicles with no apparent effect upon the incidence of severity of the reactions.

*Dr. R. Tarail, Department of Medicine, actively participated in these clinical studies.

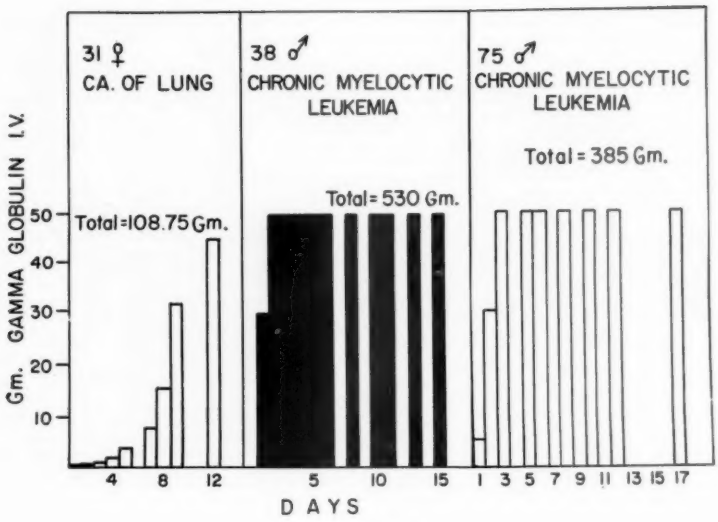


Fig. 1.

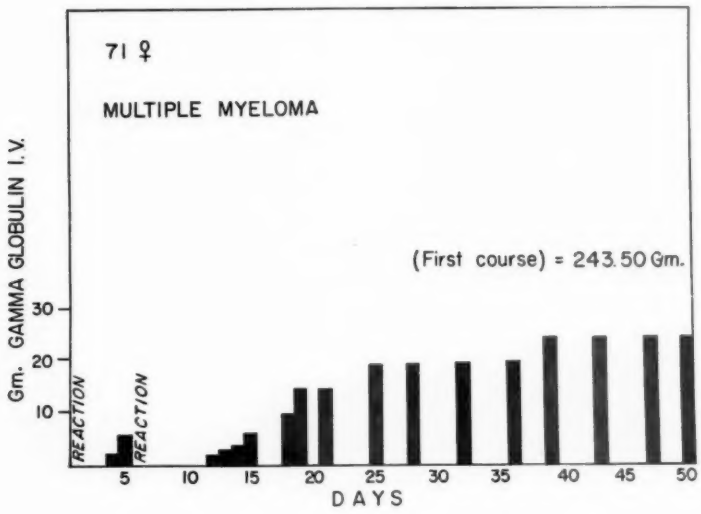


Fig. 2.

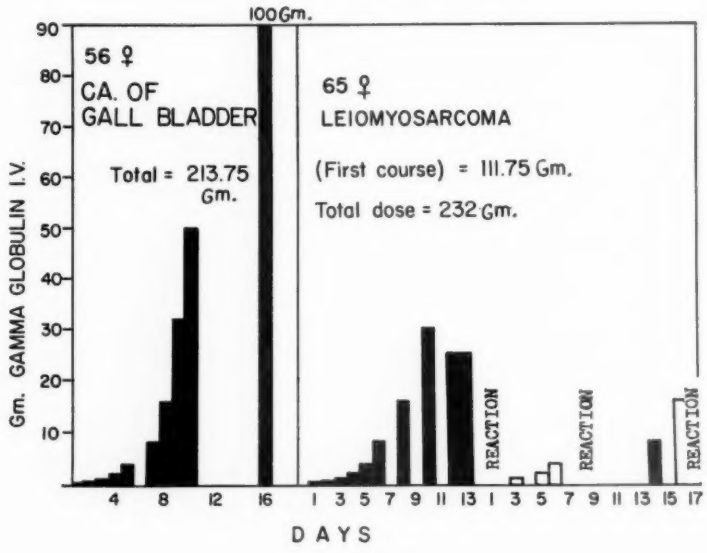


Fig. 3.

TABLE I. INTRAVENOUS GAMMA GLOBULIN

| NAME AND NUMBER | DIAGNOSIS OF PRIMARY TUMOR | DAYS OF TREATMENT | NUMBER OF INFUSIONS | GAMMA GLOBULIN IN GRAMS | REACTIONS | REACTION SEVERITY | ANTI-TUMOR EFFECT |
|---|---|---|---|---|---|---|---|
| G. U. 83952 | Carcinoma of breast | 1 | 1 | 1.0 | 1 | ++++ | - |
| S. H. 84351 | Carcinoma of lung | 12 | 9 | 108.75 | 2 | ++, ++ | - |
| W. C. 70658 | Chronic myelocytic leukemia | 15 | 11 | 530 | 0 | - | worse |
| H. M. 83453 | Leiomyosarcoma | 53 | 18 | 232 | 8 | ++, +, +, +, ++++, +, +, + | ? |
| E. C. 84712 | Multiple myeloma | 49 | 19 | 297.5 | 6 | +, +++, ++, +, ++, ++ | - |
| E. S. 84804 | Chronic lymphatic leukemia | 1 | 1 | 5 | 0 | - | - |
| L. P. 84219 | Carcinoma of pancreas | 13 | 10 | 213.75 | 4 | ++, +++, +, + | - |
| J. S. 83713 | Carcinoma of stomach | 6 | 6 | 280 | 2 | ++, + | - |
| F. F. 78611 | Chronic myelocytic leukemia | 17 | 9 | 385 | 4 | ++, ++, ++, +++ | - |
| R. B. 84060 | Carcinoma of gall bladder | 43 | 12 | 343 | 0 | - | - |
| G. D. 86057 | Hodgkin's | 5 | 4 | 64.5 | 0 | - | - |
| E. B. 53533 | Hodgkin's | 11 | 5 | 106 | 2 | +, + | - |
| F. Z. 84459 | Multiple myeloma | 26 | 11 | 400 | 1 | + | worse |

+ = Flushing, chill, slight nausea.
++ = Nausea, emesis, slight back pain.
+++ = Constriction of chest, back pain, and headache.
++++ = Severe dyspnea, cyanosis, severe back pain, and headache.

The maximum rate of infusion used in several patients without reaction approximated 50 Gm. per hour.

The largest total dose was 530 Gm. given intravenously over a period of 15 days.

The gamma globulin used in the clinical studies was the licensed commercial product. Although there were noticeable differences in the color and the appearance of the solutions of the globulin received from various pharmaceutical firms, there were no apparent differences in toxicity.

## PHYSIOLOGIC EFFECTS

Interestingly enough, there were few physiologic alterations that could be detected. Unless a severe reaction occurred, no changes in pulse, blood pressure, respiration, or temperature were noted. Hematologic studies were

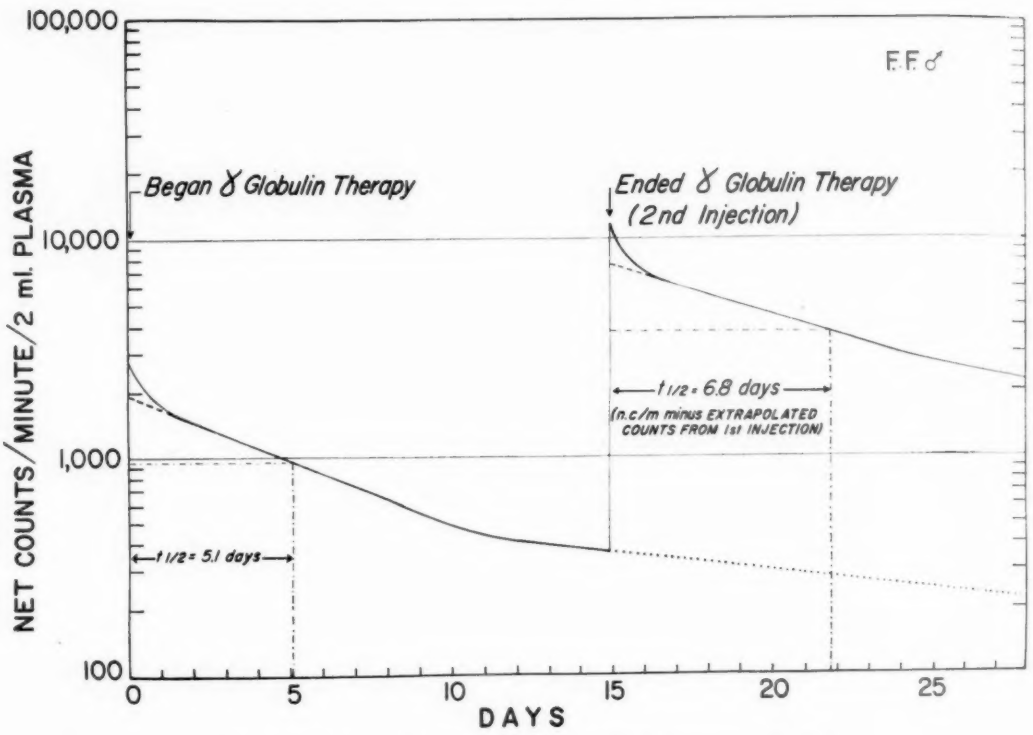


Fig. 4.—Plasma clearance of $I^{-131}$ tagged gamma globulin.

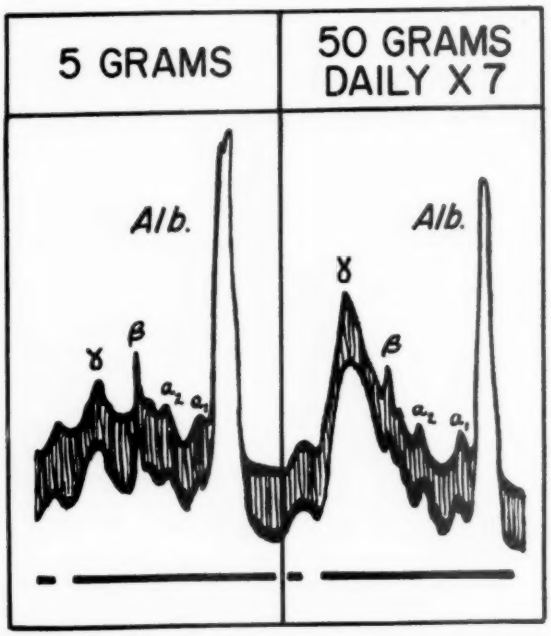


Fig. 5.—Patient F. F. Electrophoresis patterns after gamma globulin intravenously.

done before, during, and immediately following infusions of 50 Gm. of gamma globulin without finding any changes in the hemoglobin, white count, differential, or platelets.

### METABOLISM

Gamma globulin was tagged with iodine ($I^{131}$) and the serum half-life determined by Dr. M. Bender. The number of determinations were too few to be significant; however, the approximate value of 6 days is consistent with those reported in the literature. The rate of disappearance of the globulin from the blood stream was similar regardless of the amount given.

Fig. 4 represents such a study of one patient receiving 2 more widely spaced injections. After an initial injection of a tracer amount of iodinated gamma globulin, the half-life was estimated at 5.1 days. Fifteen days later, a second injection was given, and the half-life was approximately 6.8 days.

Electrophoretic studies confirmed the gross elevation of circulating gamma globulin. Fig. 5 is a record of an electrophoretic pattern obtained after 7 daily injections of 60 Gm. of gamma globulin. The levels of other serum proteins do not appear to have been affected, indicating the comparative purity of the product.

### COMPLICATIONS

Immediate reactions ranged from a mild feeling of flushing to an explosive generalized reaction with a feeling of impending doom. The milder symptoms occurring in a majority of the patients were usually immediately relieved with antihistamines or, in one instance, cortisone. When they occurred on successive days, they could be prevented by prior administration of an antihistamine or by adding it to the infusion.

Major reactions were seen in only 3 patients and consisted of a sudden collapse with "viselike" constriction of the chest, an inability to breathe or phonate, an unbearable, sharp, "sunburst" headache, and severe, sharp pain localized to the vertebral column. Despite the magnitude of the symptoms, there was only a slight transient rise in blood pressure and no change in electrocardiogram tracings or pulse rate.

The patients recovered quickly if the infusion was stopped or merely slowed, and several received equal amounts of globulin subsequently without reaction.

Similar reactions have been described with the intravenous introduction of colloidal solutions.

Table I gives a summary of the conditions treated, the dose of gamma globulin, the effect of treatment, and the incidence and nature of reactions observed.

### CHEMOTHERAPEUTIC EFFECTS

Patients with a variety of malignant tumors were included in the study. All of those with leukemia or one of the lymphomas had had previous conventional therapy and were completely restudied before initiating this study. One man showed residual effect from 6-mercaptopurine therapy. Those patients with solid tumors had metastases which could be measured directly.

There was no appreciable alteration of the lesions in any of the patients. One patient, H. M., had a recurrent leiomyosarcoma of the left retroperitoneal area and body wall which decreased markedly in size coincidental with the administration of a course of 110 Gm. of gamma globulin. Subsequently, the mass again enlarged and was not affected by further small doses of globulin. Since this tumor may have irregular growth periods, the observation was not considered significant. As previously indicated, there was no effect upon the peripheral count of leukemic cells. No favorable subjective reactions were noted and, in fact, skeletal and visceral pain in several patients which did not respond to the administration of globulin did so promptly when other chemotherapeutic agents were instituted.

Two patients with chronic myeloid leukemia and multiple myeloma, respectively, seemed to deteriorate rapidly while being given large doses of gamma globulin. The increase in both subjective and objective extension of disease prompted a shift to further treatment by chemotherapeutic agents.

## EXPERIMENTAL STUDIES

Animal experiments with whole immune serum and with fractionated serum have been carried on concurrently. It has been previously established[9] that passive immunity can be produced in mice against the C57Bl. leukemia E.L.4. Mice of 3 different strains, BALB/C, C3H, and A were given increasing doses of live leukemic cells over a period of time, the animals were sacrificed, and the sera was collected. The whole serum was then injected into untreated mice, either of the corresponding foreign strain or into the C57Bl. After a period of about 18 hours, E.L.4 cells were injected subcutaneously into all animals. In the untreated animals, tumors appeared on about the sixth day. These tumors in the foreign strains grew only temporarily and then began to regress on the ninth or tenth day. In the C57Bl. mice, the tumors continued to grow progressively and killed the animals in 18 to 20 days.

No tumors developed in mice of the 3 foreign strains protected by immune sera or, initially, in the C57Bl. In the C57Bl., the animals developed tumors after the effects of the serum had worn off. This usually took place about 10 days after similar nodules had appeared in the control mice. The tumors then grew at the same rate as in the untreated susceptible animals.

Further studies showed that absorption of the immune serum with E.L.4 leukemic cells removed the protective activity, whereas absorption with normal C57Bl. liver or fetal tissue extractions did not, although treatment with the latter tissues did remove the hemagglutinating antibodies. To explain protection in the C57Bl. mice, Gorer and Amos[8, 9] postulated the existence of a previously unknown antigen which they called "X"; this antigen was present in E.L.4 cells, but apparently, not in C57Bl. tissues.

These findings were confirmed by the present studies and X-like antigens demonstrated in 4 additional tumors, A lymphoma No. 2, C3H lymphosarcoma 6C3HED, and 2 DBA/2 lymphomas. The hyperimmune sera were prepared by a series of 3 or 4 injections of increasing numbers of live cells. Sufficient time

was allowed between the first and second injections for the transient tumor growths to regress. In a few instances, the inoculum proved to be too large and the animal was overwhelmed by tumor growth before regression could occur. The injection schedule was an initial dose of 0.5 to 0.75 million cells subcutaneously followed after 4 weeks by 20 million cells i.p., and 50 million cells i.p. 2 weeks later. Two weeks after the last injection, the animals were anesthetized and bled from the heart.

Antisera prepared in DBA/1 mice against the DBA/2 lymphoma were fractionated by sodium sulphate precipitation into 4 fractions, 0 to 12 per cent, 12 to 13.5 per cent, 13.5 to 18 per cent, and 18 to 20.3 per cent.* Hemagglutinating (H-2) activity was found to be highest in the 12 to 13.5 per cent fraction, the 0 to 12 per cent and the 18 to 20.5 per cent fractions were relatively inert both as regards hemagglutination and protection. (1) Further work was carried on with 2 fractions, 0 to 13.5 per cent containing the gamma globulin and 13.5 to 18.0 per cent including the alpha and beta globulins. The gamma globulin fraction was rich in antibodies against H-2, had high hemagglutinin activity, and would protect in DBA/1 mice, but not in DBA/2. The other fraction had low hemagglutinin activity and was found to give protection in both DBA/1 and DBA/2 mice and apparently contained the anti-X type antibody. See Table II.

TABLE II. PROTECTION AGAINST THE DBA/2 LYMPHOMA BY SODIUM SULPHATE PRECIPITATED FRACTIONS OF ANTIBODY PRODUCED AGAINST IT IN DBA/1 MICE

| PRECIPITATED BY $Na_2SO_4$ (%) | PROBABLE COMPONENT | NUMBER* SHOWING PROTECTION IN | |
|---|---|---|---|
| | | DBA/2 | DBA/1 |
| 0-13.5 | Gamma globulin | 2/10 | 10/10 |
| 13.5-18.0 | Alpha + Beta globulin | 9/10 | 9/10 |
| 18.0-20.5 | Albumin | 0/10 | 1/10 |

*Numerator indicates number of mice protected. Denominator indicates number of mice in group.

Protection afforded to the DBA/2's was temporary and lasted only for a few days, but could be prolonged by a second injection just before tumors were due to appear in the control animals. It seemed probable that the appearance of tumor nodules could be indefinitely delayed by repetitive injections of antibody. Further explanatory experiments along the line and the determination if any relationship exists between the X-type antigens of the various tumors are being continued.

## DISCUSSION

In recent years, the development of more refined biochemical, biophysical, and immunologic techniques have resulted in a renewed interest in tumor immunity.

The interesting papers by Morton and Morton[21] and Hadfield[10] are representative of the clinical literature concerning the spontaneous regression

*By Dr. Eugene Day, Department of Biochemistry.

and/or suppression of cancer which have formed the basis of the hope that perhaps, a preventive or curative immunologic approach to the cancer problem was feasible.

The history of attempts to provoke an immunologic response in humans extends back to the last century and is replete with frustration. Several of the more interesting studies are worthy of mention.

Lindstrom[18] injected the leukemic cells from patients into rabbits. The immune sera was reinjected into the patients and resulted in temporary regressions.

Stone, Curtis, and Brewer[25] prepared small cubes of tumor from the primary tumor specimen and then "killed" the tissue by keeping them at low temperatures for several days followed by reheating. The tumor specimens were implanted in the subcutaneous fat of the abdomen on alternate days. Twenty-four implants were used in each patient. Several instances of growth of the implants occurred indicating that not all of the cells were killed. No effect upon the patients' malignant disease was noted.

An excellent review by Hauschka[11] summarized the status of research pertaining to immunity and tissue specificity. Articles by Woglom[27] and Spencer[24] cover much of the earlier experimental work.

It is noteworthy that an interesting series of experiments by Kaliss and his co-workers[14-16] has revealed an enhancing effect of tumor antisera which is contrary to the inhibiting effect noted in our experiments! The enhancing factor was found to be associated with the globulins and was most concentrated in the gamma globulin fraction. They concluded that the substance was an antibody component.[16]

The same antibodies may, therefore, inhibit or enhance the growth of transplanted tumors or grafts. A possible explanation of this phenomenon is a difference in dosage of antibody, although the genetic relationship of the host and the transplanted tissue also appear critical. The enhancing effect may result from a combination of the passively transferred antibody with antigen of the tumor so that the immunologic response of the host is weakened or delayed.

In addition, both the XYZ effect of Casey[4] and the enhancement of Snell[23] appear to depend upon the modification of the actual tumor cells. Casey and his co-workers[4] found that the second transplant after treatment of the original host with frozen tumor showed a modified XYZ effect with accelerated growth in the earlier stages after transplantation. Kaliss[15] reported progressive growth of an enhanced tumor in untreated foreign strain mice normally resistant to S.A.1, but the altered specificity did not appear to be permanent.

The alteration appears to be mediated by an unfavorable, although not lethal environment; the ability to respond seems to reside in a relatively limited number of tumors. Recently, Mirand and his associates[19] have shown a similar change with the DBA/2 lymphoma of Dalton after passage through an embryonated egg, while this same tumor has, in some of our experiments, grown

and killed DBA/1 mice after an unusually prolonged course of immunizing injections. In this case, although the mice had a good antibody titer, the tumor itself appeared nonantigenic in that it failed to absorb antibody, and would, therefore, be expected to be immunologically inert. This modified tumor did not kill either C57Bl. or C3H mice.

Transferred antibody or the development of an immune state may then, if it fails to kill the tumor cells, lead to the emergence of a permanently altered variant by immunoselection[12] or to a temporarily modified cell which loses its resistance upon transplantation. The mechanism of this alteration is at present unknown, but it is doubtful if this is an example of adaptation[2] as has been suggested by Kaliss.[15] It may be merely due to a combination of "blocking" antibody with surface antigens. In the present experiments, administration of globulins pooled from many animals must be considered a massive dose of antibody which probably not only neutralizes the tumor antigen but also directly affects the malignant cells.

Pressman[22] has utilized radioactive isotopes to tag antitumor antibodies and to demonstrate that such antibodies do actually localize in the tumor, while antibodies to other tissues localize only weakly in the tumor, indicating that there are unique antibodies in the antitumor serum.

Recent work by Day and associates[5] indicates that at least in a rat lymphosarcoma there is a substance which differs antigenically from components of normal rat tissues. Tumor antibody preparations do contain components capable of localizing in other tissues but these can be removed by specific purification procedures.

From animal experiments, it would appear that further attempts to characterize tumor immunity in humans should be directed toward leukemia rather than the solid tumors so as to avoid the antigenicity associated with the accompanying stroma. Further, if the experimental studies are transposable to man (a risky assumption), it would seem that a therapeutic effect rather than enhancement of growth would be more likely to be obtained with the leukemias.

Still another immune process may be operating in host resistance to the implantation of malignant cells which resembles the tuberculin type of allergic reaction. In such an instance, cellular antibodies are involved and transfer can only be accomplished by the transfer of viable cells of the lymphoid series.[20] Such antibodies would be available for action against the tumor cells only after migration of the cells into the tumor from the blood stream of the host.

The experiments of Algire and his co-workers in which tumor fragments were placed in millipore chambers inserted in the abdominal cavity of immunized mice are germane to this point. When membranes of large pore size were used, lymphocytes entered the chamber and the tumor cells were rapidly destroyed. If chamber membranes with small pore size were used, lymphocytes were excluded and the tumor cells survived. Unfortunately, it is not known to what extent cells or antibody participated. In the former experiment, both cells and antibody must have entered the chamber and in the latter, although

cells could not enter, it is uncertain whether antibody could do so in effective amounts. An experiment in which empty chambers were placed in the abdominal cavity of mice immunized against sheep cells showed that the antibody concentration reached inside the chamber was only about one-fifth of the concentration in the serum.[26]

The foregoing can be summarized as follows: (1) For some tumors, passively transferred antibodies alone are inhibitory to the cells. (2) Other tumors appear to be only partially affected by antibodies but are killed when in combination with other unidentified resistance factors. These factors may be sessile antibodies brought to the tumor by lymphocytic cells of the host. (3) In the presence of inadequate amounts of antibody, the antigens of the tumor may be neutralized preventing an immune response by the host. Under these circumstances, enhanced tumor growth may result.

## CONCLUSIONS

1. The intravenous injection of large doses of human gamma globulin was accomplished in 13 cancer patients with only 3 severe reactions. No antitumor effects were seen. Two patients with leukemia may have been adversely affected.

2. Hyperimmune sera and more specifically, their globulin fractions afforded excellent protection against the subsequent injection of leukemic cells in certain strains of mice.

3. The possibility of future clinical investigations and the implications of present experiments in cancer immunity are briefly discussed.

Further studies to isolate, quantitate, and identify both the antigens and antibodies of tumors should certainly be done. The ultimate goal would be the complete isolation of antibodies so specific that they would selectively kill only the malignant cells irrespective of the genetic constitution of the host.

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# SIMPLIFIED TECHNIQUE FOR ILEOSTOMY CONSTRUCTION

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OF THE many types of ileostomy stomata which have been described, Brooke's,[1] with the complete 2-thickness ileostomy, until recently has been the most satisfactory in the prevention of skin strictures. This has been modified by Crile and Turnbull[2] into the mucosal-grafted ileostomy. The mucosal-grafted ileostomy has the advantage of preventing ileostomy obstruction and cicatrix about the stoma, as well as the fact that it can be immediately utilized with a temporary ileostomy bag. Also, the permanent bag can be fitted much more quickly in the postoperative course.

However, the procedure has a distinct disadvantage in that stripping off the seromuscular layer is much more difficult to do than it would seem from the technique as described. This is especially true when there is an associated serositis, frequently present in those cases coming to ileostomy. Also, along the mesenteric border the musculature strips away with even more difficulty. While perforation of the mucosa does not necessarily cause failure of the procedure, there does occur an increased tendency to scar formation and consequent stricture. There is marked discoloration of the reversed mucous membrane because of loss of its blood supply, and, in effect, while having some blood supply submucosally, it is almost a free graft except at the edge where it joins the ileum proper. In order to overcome these objections, the following technique was devised.

A circular portion of skin, fat, and superficial fascia is excised from the appropriate site of the right lower quadrant. The fascial layers are split longitudinally; if their edges are sharp, a portion is removed to prevent any tightness about the ileum. Likewise, if the ileum happens to be brought through at the edge of the rectus sheath, its edge is cut so as to prevent stricture within the abdominal wall. The mesentery of the ileum is then fastened to the lateral abdominal wall to prevent herniation lateral to the ileum.

Rather than completely strip the muscular layers from the mucous membrane, 4 longitudinal slits are made through the musculature of the terminal one inch of the ileum. An additional inch of ileum with its musculature undivided exists above the skin level (Fig. 1). Similar to the Rammstedt pyloroplasty, the mucous membrane immediately bulges in these areas as soon as the muscles are cut so that there is no stricturing of the stoma from the limitation of its diameter by the outer layer. The incised portion of the ileum is then reversed and sutured to the skin margin with a few interrupted fine chromic sutures.

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The procedure is advantageous because it can be done in a few seconds instead of several minutes. The blood supply is not significantly disturbed and the ileostomy retains a normal, healthy appearance. A temporary ileostomy bag can be applied immediately to the abdominal wall, and the ileostomy functions as satisfactorily on the first day as it does several days later. With less manipulation of the bowel there is much less postoperative edema.

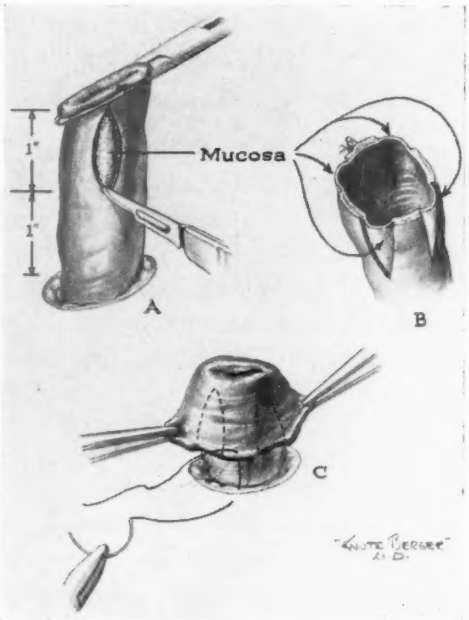


Fig. 1.

We used the mucosal-grafted technique in 5 consecutive ileostomies and total colectomies with satisfactory results except that it was considerably more time consuming and there was more edema and a less healthy appearance of the stoma. The described method has also been used in 6 consecutive procedures of the same type with even more satisfactory results because of its speed, simplicity, minimal manipulation, and better blood supply. While this simplified technique has worked well in our hands, we hope that it will be applied by others with larger series in order to get a more accurate appraisal of its worth.

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# NONSUTURE CLOSURE OF CLEAN MUSCLE-SPLITTING ABDOMINAL WOUNDS

## Preliminary Report of 117 Wounds

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As a result of the favorable findings in previous studies of abdominal incisions and the effects of early ambulation on wound healing, a study series of nonsuture of certain abdominal incisions was begun in September, 1954.[1-14]

Because normal muscle pull of the anterolateral group of abdominal muscles is strongest in the direction of their fibers, that is, laterally away from the midline, an incision paralleling these muscle fibers should be normally reapproximated by its own muscular pull and force, and this unit force should maintain any properly placed incision in apposition. Therefore, a correctly oriented wound which has not injured the main nerve and blood supply should heal solidly with a minimal chance for evisceration or postoperative herniation without the necessity of suturing.

The incidence of abdominal wound complications, namely dehiscence and herniation, has ranged between 2 and 10 per cent when a midline or paramedian incision is employed.[1, 5, 6, 10, 12-14] However, when a more anatomically and physiologically sound incision is employed, that is, a muscle-splitting or a transverse type, these complications are rare, occurring in less than 1 per cent of all cases.[1, 4-12, 14]

Readily apparent to any surgeon who has used a muscle-splitting or transverse incision is the fact that the force exerted by the group of muscles in the anterolateral abdominal wall (external and internal oblique and transversus) is very great. On occasions when the plane of anesthesia was light or the agents employed were only partially effective, the surgeon has found the muscular contractions so strong that he was unable to insert his hand or remove it from the wound. The natural protective response of muscle contraction to splint and guard these wounds should be sufficient to maintain integrity of the closure when the anesthesia has worn off during bed rest and ambulation.

Based on this rationale and encouraged by the statistical incidence in favor of the muscle-splitting incision, a series of wound closures was started in which the muscle layers of McBurney type incisions and transverse midabdominal incisions were not sutured. In 117 consecutive wounds in 98 adult men, closure consisted of fine nonabsorbable silk or catgut sutures in the peritoneum, subcutaneous fascia, and skin. The muscle layers were allowed to reapproximate themselves of their own accord.

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The technique and portrayal of a transverse muscle-splitting midabdominal incision as used in this study have been reported elsewhere.[5, 6]

## RESULTS

The cases included in this study were consecutive male patients from the ages of 20 to 71 years who were operated upon for acute or recurrent appendicitis through a McBurney incision or upon whom a lumbar sympathectomy was performed through a midabdominal transverse muscle-splitting incision for a variety of vascular diseases or conditions of the lower extremities.

TABLE I. AGE INCIDENCE

| AGE | NUMBER | PER CENT |
|---|---|---|
| 20-30 | 34 | 29.0 |
| 31-40 | 19 | 16.2 |
| 41-50 | 8 | 7.0 |
| 51-60 | 23 | 19.6 |
| 61-70 | 30 | 25.6 |
| Over 70 | 3 | 2.5 |

Of the 117 incisions, 51 were of the McBurney type and 66 were of the transverse muscle-splitting type.

The suture material utilized for closure of the peritoneum was 3-0 chromic catgut in all cases. The subcutaneous fascia was closed with 3-0 chromic catgut in 26 cases and 4-0 silk in the remaining number. The skin closure in all cases was accomplished with 3-0 silk. The skin sutures were removed on the fifth postoperative day in the McBurney type incisions and on the seventh day for the midabdominal transverse incisions.

Early ambulation was practiced in all cases except 2; one, because of frostbite of the feet and the other patient, because of flexion contracture of both hips. This regime, consisting of getting the patient up and walking him, had all these patients ambulatory within 24 hours; most of them, within 12 hours. The activity and its duration were increased each day.

TABLE II. DAY OF AMBULATION

| AMBULATORY DAY | NUMBER | PER CENT |
|---|---|---|
| Day of surgery | 20 | 17.5 |
| 1st P.O. | 92 | 80.7 |
| 2nd P.O. | 2 | 1.1 |

All surgical dressings were removed from these wounds within 24 hours, and the wounds were left uncovered and without protection thereafter. The results of nonsurgical dressings of clean abdominal wounds have been reported elsewhere.[9]

A follow-up was obtained in 90 per cent of the cases; the remainder were not obtainable because the patients had moved or were on active military duty. The follow-up period was from 3 to 18 months.

The 2 local wound complications, infection and seroma or hematoma, developed as would be expected with any wound. However, the incidence of seroma

TABLE III. FOLLOW-UP

| MONTHS | NUMBER | PER CENT |
|---|---|---|
| 18 | 5 | 4.7 |
| 12 | 29 | 27.5 |
| 6 | 40 | 38.0 |
| 3 | 20 | 19.0 |

or hematoma (9.4 per cent) was much higher than in our previous report on muscle-splitting incisions (1.5 per cent) that were closed by the layer-to-layer suture method.[5, 6] This complication became less frequent as greater care was exercised to control bleeding from the muscles. Of the 11 wound seromas or hematomas, 10 occurred with the transverse midabdominal muscle-splitting incision.

Wound infection occurred in only one case (0.8 per cent) and followed an appendectomy through a McBurney incision. Wound dehiscence did not occur in any of the cases in either group. There were 2 postoperative hernias in the transverse midabdominal group. In our opinion, both these patients would most likely have developed hernias even if a suture type closure had been employed. One patient, 67 years of age, was very obese and had a redundant and relaxed abdominal wall; the other patient, 58 years of age, was a bedridden arthritic. None occurred in the McBurney group.

The incidence of incisional hernia was 2.5 per cent as compared to 0.37 per cent in a muscle-layer closure with silk.[5] However, selection criteria makes possible the assumption that the incidence of postoperative herniation will be no higher than that reported above in routine muscle layer closure.

## COMMENT

It appears from this study and follow-up that the abdominal wounds which are muscle-splitting in type and are made layer by layer in the direction of the muscle fibers and their pull do not require suturing for a safe wound closure. This is with the provision that there is no injury to the main nerve and blood supply to these layers.

The normal muscle contraction, in the direction of its long axis, will reapproximate itself so that any linear incision or opening will no longer exist with resumption of normal muscle tone. Any incision, however, made in the aponeurosis of the external abdominal oblique muscle or the anterior rectus sheath should be closed by fine nonabsorbable suture material. In this series in many cases, this was not done; no hernias developed through these aponeurotic defects; however, these areas eventually healed solidly. It is our policy now to suture all aponeurotic defects but we do not suture the muscle layers.

The nonsuture technique shortens the operating time and reduces the amount of fibrosis associated with healing as well as the degree of tissue reaction which occurs secondary to suture material utilized with normal wound closure. This new method encourages a more normal tissue response associated with good wound healing.

This technique is recommended in all patients who are good risks, who are in good nutritional status, who are not obese or bedridden, and whose wounds

are not contaminated at the time of surgery because of surgical technique or underlying pathology.

SUMMARY

Properly performed McBurney and transverse midabdominal muscle-splitting incisions do not require suture closure of the muscle layers. Suture closure of the peritoneum, superficial fascia, and skin is all that appears necessary. There were no cases of dehiscence in either type of abdominal incision. Postoperative incisional hernia did not occur except in 2 patients who most likely would have developed this complication even with a suture muscle layer closure of their wounds; none occurred in the McBurney incision group.

Ninety-eight consecutive male patients (117 abdominal wounds), ranging from 20 to 71 years of age, who were being operated upon for acute or recurrent appendicitis through a McBurney incision and those undergoing lumbar sympathectomy for a variety of vascular diseases were included in this study.

The normal muscular pull and force, in the direction of their fibers, will normally hold a properly placed incision in approximation without the need of suture material since the natural protective muscular tone and contraction maintains a secure closure of the surgical defect.

Wound complications are similar in type and degree to those with other wound closures. Care should be taken to obtain good hemostasis, particularly in the muscle layers.

This nonsuture technique is not advocated for the debilitated, poor risk, or obese patient or for one who has a large relaxed abdominal wall.

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# THE UTILIZATION OF THE RECTUS MUSCLE AS A PEDICLE FLAP IN CLOSURE OF PELVIC DEFECTS

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CONFRONTED with the problem of reconstruction of the pelvic floor in cases of total evisceration of the pelvic organs, we have devised a simple technique of closure not known to be previously reported. We have felt it preferable to prevent herniation of the small bowel into the denuded true pelvis. Closure of the pelvic defect by standard techniques is often impossible when wide excision of the peritoneum has been performed. Some type of the reconstruction is, of course, mandatory if the exenteration has necessitated an extensive excision of the perineum.

*Technique.*—Our technique involves the use of one or both rectus abdominis muscles turned down as a pedicle flap. Enough length is used so that the flap may be sutured posteriorly in the region of the promontory of the sacrum and laterally along the iliopectineal lines or to the peritoneum of the iliac fossae. Such pedicles have excellent blood supply if care is taken to spare the deep inferior epigastric vessels. When both muscles are used, they are sutured to each other in the midline. In this way a very adequate substitute pelvic diaphragm may be constructed. (See Fig. 1.) In the situation where the perineum must be left open, the flap may be supported from below by a pelvic pack. The anterior rectus sheath is not disturbed. The abdominal wound is closed with interrupted silk sutures to the anterior rectus sheath and through-and-through sutures of stainless steel wire catching all layers of the abdominal wound, thus obliterating dead space and relieving tension on the fascial suture line.

## CASE REPORTS

CASE 1.—An anterior exenteration, sigmoid colostomy, and reimplantation of the ureters into the rectum were carried out, on Dec. 16, 1954, under hypotensive anesthesia through a combined abdominal and perineal approach for an extensive Grade 3 papillary carcinoma of the bladder that had extended beyond the bladder wall invading the prostatic urethra in a 54-year-old man. A single rectus flap was turned down to bridge the gap of the peritoneal closure and was packed from below through the perineal wound. Eighteen months following surgery, the abdominal wound has healed firmly without hernia, the perineal wound has filled in completely, and there has been no evidence of bowel obstruction.

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CASE 2.—A 60-year-old man had a total pelvic exenteration, on March 7, 1955, under hypotensive anesthesia after preliminary emergency cutaneous ureterostomies. He had a massive, infiltrating, bleeding papillary carcinoma of the bladder with perirectal, perivesical, and prostatic local extension. It was necessary to use both rectus muscles as flaps sutured together to close the peritoneal defect and to wall out the small bowel from the denuded pelvis. Again, a pelvic pack was placed. The patient succumbed on the eleventh postoperative day following hemorrhage from a "stress" ulcer that had eroded the gastroduodenal artery. At post-mortem examination, the reconstructed pelvic floor was found to be intact with viable muscle flaps.

CASE 3.—A 33-year-old white woman had a Stage III carcinoma of the cervix uteri which had been treated with radium implantation and deep x-ray therapy one year earlier. On March 7, 1956, a total pelvic exenteration for recurrent tumor and extensive x-ray necrosis were performed. The ureters were implanted into an isolated ileal pouch. It was necessary to reconstruct the pelvic floor because the operation had been performed through a combined abdominoperineal approach. The reconstruction of the pelvis was successfully accomplished using a right rectus muscle flap supported from below by a pelvic pack. The patient expired 2½ months later from hepatitis with a complicated postoperative course. However, the flap remained intact and could be inspected from below through the perineal wound. At post-mortem examination it was demonstrated to have remained viable and had healed as a substitute diaphragm.

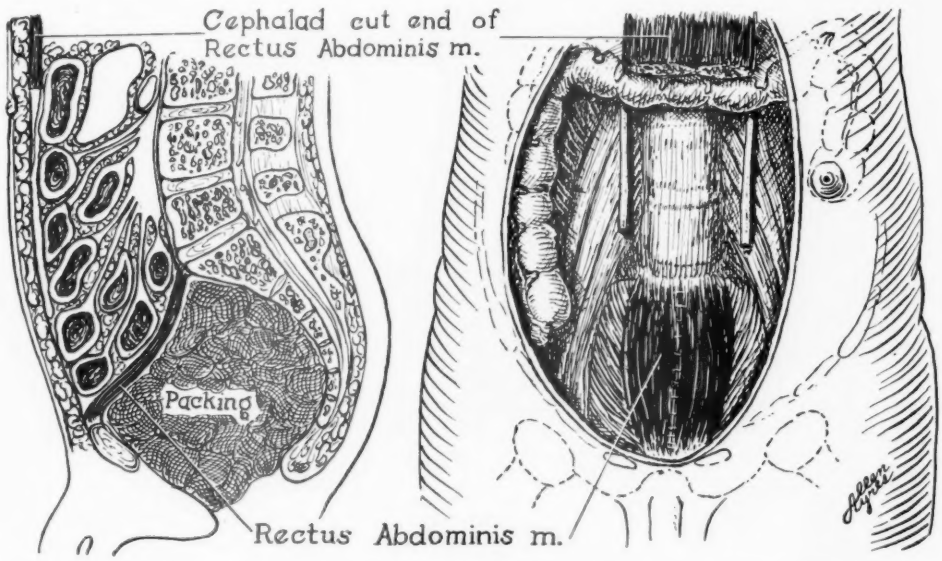


Fig. 1.—Diagram of position of rectus flap after suture to the promontory of the sacrum and the brim of the true pelvis laterally.

It occurred to us that this technique might be further used in repairing certain difficult vesicovaginal, vesicorectal, or rectovaginal fistulas. Such a rectus muscle pedicle flap might be interposed to repair a relatively avascular defect from extensive destruction of tissue and fascia in the pelvic area. Bastiaanse[1] has reported the use of pedicle flap of omentum in this connection.

## SUMMARY

A brief report is made of a technique for reconstructing the pelvic floor after extensive surgery. This technique involves use of a pedicle flap of one or

both rectus muscles. Further application of this principle is suggested in the repair of fistulas between adjacent pelvic viscera.

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# AN EVALUATION IN THE DOG OF CARDIAC SPHINCTER SUBSTITUTION BY INTERPOSED COLON IN THE PRESENCE OF VAGOTOMY AND FINNEY PYLOROPLASTY

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IN THE dog, postoperative esophagitis inevitably occurs after the cardiac sphincter is excised, despite other ancillary procedures such as pyloroplasty, vagotomy, gastroenterostomy, partial upper gastrectomy, and valvular esophagogastrostomy.[5-7] That the esophagus of this animal is extremely sensitive to acid-pepsin allows an excellent testing ground for the evaluation of any operative procedure on the cardiac sphincter. Jejunal segments interposed between the lower esophagus and stomach have satisfied the criteria for an ideal substitute sphincter.[1, 4, 8] Whereas the jejunum has been adequately studied, little is known of the response of the colon when interposed between lower esophagus and stomach. Intestinal sensitivity studies have shown that the colon as well as other levels in the gastrointestinal tract actually have no increased inherent sensitivity to acid-peptic digestion and ulceration.[2, 3] If this be the case, the results of esophageal or sphincter replacement by either small intestine or colonic segments should be reasonably similar. Sirak and his co-workers, however, concluded that colon segments interposed between the esophagus and stomach showed more tendency toward erosion and perforation than the jejunum and was therefore inferior to the jejunum, though the sphincteric properties of both prevented esophagitis.[10] In their preparation the vagi and pylorus were left intact.

Though vagotomy exerts no influence in the prevention of esophagitis, it was incorporated in our preparation for two reasons. Oftentimes its sacrifice is inevitable at operation where severe periesophageal fibrosis accompanies benign ulcerative esophagitis. Secondly, because histamine stimulation provokes an increased gastric secretory response with intact vagi, the survival period is reduced as a result of gastric and/or duodenal perforations.[4] Thus, by bilateral vagotomy the response to histamine is ameliorated allowing a more prolonged exposure of the esophagus to possible contact with acid-pepsin and a more valid test. A Finney pyloroplasty is carried out to provide adequate gastric drainage.[9]

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With a preparation identical to that in which jejunal interposed segments were previously tested, a direct comparison is possible of the jejunum and colon with regard to sphincter properties and acid-pepsin resistance.

## METHOD

Large mongrel dogs were anesthetized with intravenous Nembutal and connected to the Palmer respirator by means of an endotracheal tube. Through an upper midline incision, the lower 2 cm. of the esophagus and esophagogastric junction were excised. Both vagi were sectioned. After closing the stomach, a carefully selected segment of colon with intact vasculature was isolated and moved up into the subphrenic region posterior to the stomach. The pedicle had to originate from one or two of the right colic vessels, since the midcolic artery must be preserved in the dog. In over 80 per cent of the animals examined, the left colic artery is unable to support the left or descending colon. The segments varied from 9 to 13.5 cm. in length. Open 2-layer anastomoses were carried out with the colon isoperistaltic to the esophagus. A neocologastrostomy was performed on the anterior wall of the cardia. End-to-end anastomosis utilizing a single-layer closed technique restored large bowel continuity. A 2-layer Finney pyloroplasty making the orifice at least 4 cm. completed the basic preparation.

Fourteen animals were prepared in this fashion. For 5 days postoperatively, each animal received antibiotics and parenteral fluids by clysis, withholding oral alimentation. Clear liquids were started on the sixth day, gradually increasing the solidity of a basic soft diet to full caloric rations of osterized Friskies and milk. Weight loss was marked during the first 2 weeks, averaging 2 to 4 Kg., but by the end of a 30-day period all animals were eating a semisolid diet without difficulty and weight loss ceased.

Following a 30-day minimum recovery period, all animals were esophagoscoped and the appearance of the esophagus and colon was noted. Thirty milligrams of histamine in oil and beeswax were given daily until the animal died or a 45-day period elapsed. During this interval, 5 animals were x-rayed with contrast barium and apomorphine administered intramuscularly. Histologic sections were taken from several parts of the esophagus and colon on all specimens at the time of spontaneous death or sacrifice. Photographs were taken of significant and representative specimens.

## RESULTS

*Esophagus.*—There was complete absence of any esophagitis in this series (Fig. 1). Sections of esophagus 8 cm. proximal to the esophagocolon anastomosis and sections adjacent to this anastomosis failed to show any squamous cell destruction or erosion. Submucosal glands of the lower esophagus, prone to show early and minute changes in early esophagitis, were unaltered.

*Colon.*—In 11 of the specimens examined, no mucosal changes were present, even at the more heavily exposed gastrocolic junction. Mucous production by the glandular elements of the colon was sufficiently intact as to produce a characteristic mucosal film. Two of the colon segments showed evidence of erosion, but without frank ulceration. The third, that of T-11,

though surviving 45 days under histamine stimulation, had an old, sealed perforation of the colon adjacent to the gastrocolic anastomosis. Suture line breakdown with a small leak instead of actual acid-peptic digestion of colon wall may have occurred. The remaining colon mucosa was entirely free of ulceration.

The total functioning length of each segment at autopsy was reduced approximately 15 per cent over the initial length through serosal adhesions and scarring. Regardless of foreshortening, the peristaltic activity of each segment was sufficient to protect against esophagitis in these animals.

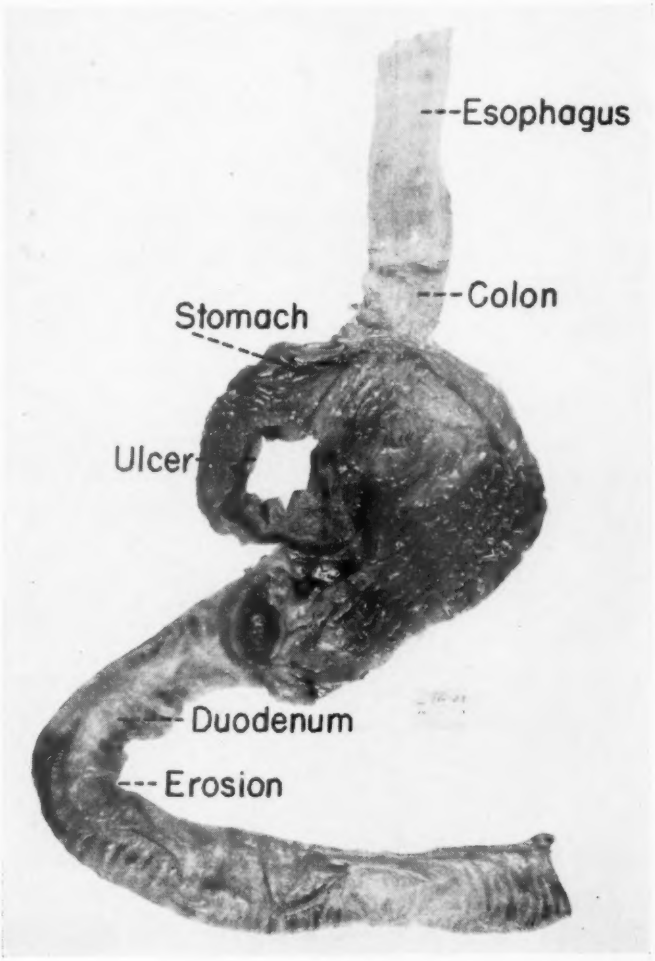


Fig. 1.—Post-mortem specimen showing massive gastric ulcer and duodenal erosion after 43 days of intense histamine stimulation. There is no colon segment or esophageal pathology.

The minimal pathology of the interposed colon segments as well as the similarity of the other results when compared with jejunal segments are shown in Table I.

*Stomach and Duodenum.*—On chronic histamine stimulation, gastric ulcerations were present in 50 per cent of the animals, with perforations in 21 per cent. Duodenal ulceration was present in 70 per cent of the dogs, again

TABLE I. COMPARATIVE RESULTS BETWEEN COLON AND JEJUNUM INTERPOSITION OPERATIONS IN THE DOG

| OPERATION | AVERAGE DAYS | | | PERCENTAGE PATHOLOGY | | | | |
|---|---|---|---|---|---|---|---|---|
| | ANIMALS | HISTAMINE | TOTAL SURVIVAL | ESOPHAGUS | JEJUNUM | COLON | STOMACH | DUODENUM |
| Jejunal interposition with vagotomy and Finney pyloroplasty[8] | 10 | 25.2 | 55.4 | 0 | 10% ulc.*<br>No perf. | ---------- | 50% ulc.<br>20% perf. | 40% ulc.<br>20% perf. |
| Colon interposition with vagotomy and Finney pyloroplasty | 14 | 24.8 | 59.9 | 0 | -------- | 14% erosion**<br>7.1% perf. | 50% ulc.<br>21% perf. | 70% ulc.<br>21% perf. |

*Animal with jejunal ulcer died of perforated duodenal ulcer

**Two animals with colonic erosion had multiple duodenal ulcers and perforated duodenal ulcer, respectively; animal with perforated colon segment (discussed in text) had large single duodenal ulcer.

TABLE II. SUMMARY OF PROCEDURES AND RESULTS

| DOG NO. | POSTOPERATIVE SURVIVAL DAYS | | | LENGTHS OF COLON SEGMENTS IN CENTIMETERS | GROSS AND MICROSCOPIC RESULTS | | | | COMMENT |
|---|---|---|---|---|---|---|---|---|---|
| | PRIOR TO HISTAMINE | DURING HISTAMINE | TOTAL SURVIVAL | | ESOPHAGUS | COLON | STOMACH | DUODENUM | |
| T-2 | 48 | 45 | 93 | 9.5 | N | N | N | N | Sacrificed |
| T-4 | 46 | 4 | 50 | 8.3 | N | N | P | N | Perforated gastric ulcer |
| T-5 | 45 | 4 | 49 | 9.0 | N | N | N | P | Perforated duodenal ulcer |
| T-11 | 35 | 45 | 80 | 12.0 | N | P | N | U | Sacrificed (perforation sealed) |
| T-12 | 34 | 11 | 45 | 11.5 | N | N | U | P | Perforated duodenal ulcer |
| T-16 | 31 | 2 | 33 | 12.0 | N | N | N | N | Starvation and emaciation |
| T-17 | 31 | 12 | 43 | 11.5 | N | N | U(s) | U | Incarcerated diaphragmatic hernia |
| T-18 | 31 | 40 | 71 | 13.0 | N | N | U(s) | U(s) | Bilateral pneumonia |
| T-19 | 31 | 45 | 76 | 11.0 | N | E | N | U(s) | Sacrificed |
| T-20 | 31 | 45 | 76 | 10.5 | N | N | E | U(s) | Sacrificed |
| T-21 | 30 | 18 | 48 | 11.5 | N | N | N | N | Starvation and emaciation |
| T-23 | 35 | 43 | 78 | 11.0 | N | N | P | E | Perforated gastric ulcer |
| T-26 | 31 | 13 | 44 | 10.0 | N | N | P | E | Perforated gastric ulcer |
| T-27 | 34 | 20 | 54 | 10.8 | N | E | N | P | Perforated duodenal ulcer |

E—Erosion
N—Normal
P—Perforated ulcer
U—Ulcer; (s)—more than one ulcer

with a 21 per cent perforation rate. As seen in Table II, erosion and perforation of the colon occurred in these animals but only in the presence of severe ulcerative disease or perforation of the stomach and duodenum.

### MISCELLANEOUS

Gastrointestinal barium x-rays were carried out in 5 animals surviving the histamine test period of 45 days. No appreciable stasis of the barium bolus occurred in the colon segment, due in part to the relative shortness of the interposed colon and the unusually strong peristaltic waves of the dog's large bowel.

Apomorphine sulfate, 0.1 mg. per kilogram, was administered intramuscularly to these 5 dogs. Regurgitation efforts, salivation, and air swallowing resulted, but none of the animals vomited gastric contents or barium. X-rays failed to delineate the colon after this test, though the stomach was filled with barium.

### DISCUSSION

When vagotomy and pyloroplasty accompany colon or jejunal interposition operations, the results show a striking similarity. Except for one perforation in the colon series, the statistical analysis of pathology in the upper gastrointestinal tract is nearly the same. With complete absence of esophagitis in the experimental preparation and minimal mucosal reaction of the colon to acid-pepsin, the colon appears to be as satisfactory as the jejunum for replacing the cardiac sphincter. Thus, supportive evidence again is present corroborating the new concept of equal resistance of the intestinal tract to acid-peptic digestion.

For the purpose of sphincter substitution, the jejunum is ideal; however, when long segments are needed for esophageal replacement, a distinct advantage of the colon over the jejunum is that it remains a straight tube, whereas it is impossible to remove completely jejunal redundancy with long segments. That the colon will resist acid-peptic digestion is important, since ulceration, hemorrhage, stricture, and perforation are thereby avoided.

### CONCLUSIONS

1. Fourteen dogs had segments of colon interposed between the lower end of the esophagus and stomach after the excision of the cardiac sphincter. Bilateral vagotomy and Finney pyloroplasty accompanied the procedure.

2. Under intense histamine stimulation, esophagitis was completely prevented by the interposed colon.

3. The colon "sphincter" displayed intrinsic mucosal resistance similar to that of previously tested interposed jejunal segments in identical preparations. This finding tends to support the new concept of equal resistance of various levels of the intestinal tract to acid-peptic digestion.

4. The colon in its new position exhibits greater resistance to acid-peptic digestion than either the stomach or duodenum.

5. The administration of apomorphine to these animals did not result in any detectable lesions in the gastrointestinal tract in spite of their inability to vomit.

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# JOINT PARACENTESIS FROM AN ANATOMIC POINT OF VIEW

## II. Hip, Knee, Ankle, and Foot

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### INTRODUCTION

TECHNIQUES for paracentesis are to be found in a number of places (Albee,[1] Kling,[8] Mawson,[11] Speed and Smith,[19] Hollander and associates,[3-7] and Sperling[20]). However, since in certain instances it appeared that better sites might be found and that easier landmarks might be used, an anatomic study of joints commonly aspirated or injected was made with these ends in view.

In the first paper of this series (Miller[12]) the principles for selecting sites for paracentesis were stated and sites were recommended for the shoulder, elbow, wrist, and hand articulations. The present report deals with the results of anatomic studies on the articulations of the inferior extremity.

### CRITERIA CONSIDERED IN SELECTING SITES FOR PARACENTESIS

According to the principles developed in the first paper of this series, the following considerations have been taken into account in selecting injection sites for the inferior extremity:

1. The site should be as far removed as possible from tendons, large nerves, or blood vessels.
2. A palpable bony landmark should be available in the immediate vicinity of the injection site.
3. If the landmark is not easily palpable when the joint is in the best position for injection, the joint may be palpated in one position and subsequently moved to the position for injection.
4. Methods such as distraction or positioning which will enlarge the target area (the joint cavity) should be utilized.
5. Positioning should be such as to stretch the part of the capsule and any supporting ligaments that might be penetrated by the needle tip.
6. The direction of penetration should be such as to minimize the danger of scoring the articular cartilages.

### ANATOMIC RATIONALE FOR APPROACHES TO JOINTS OF THE INFERIOR EXTREMITY

A. *The Hip Joint.*—Even in the hands of the most experienced this is the most difficult of all joints and more than 50 per cent failures in injection are

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Reported in abstract form (Miller, Pruce, and Berger[14]).

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reported (Hollander,[3-5, 7]). Since Hollander himself suggests that failure of a given joint to respond to therapy "may be due to faulty injection technique with the hormone not having been placed directly in the synovial cavity" (p. 357), it would appear that the search for a better injection site for this joint is well justified.

The difficulties in the case of the hip derive from its distance from the skin and the lack of bony landmarks in close proximity to the target area. Several approaches have been tried. The anterior (described by Pels-Leusden,[15] Schmeiden,[17] and more recently by Hollander) is most frequently used. Several versions of the lateral approach have been described (Krause,[9] Hollander,[4, 5] Landsmeer and Koumans,[10] and Sperling[20]), and there is even a pos-

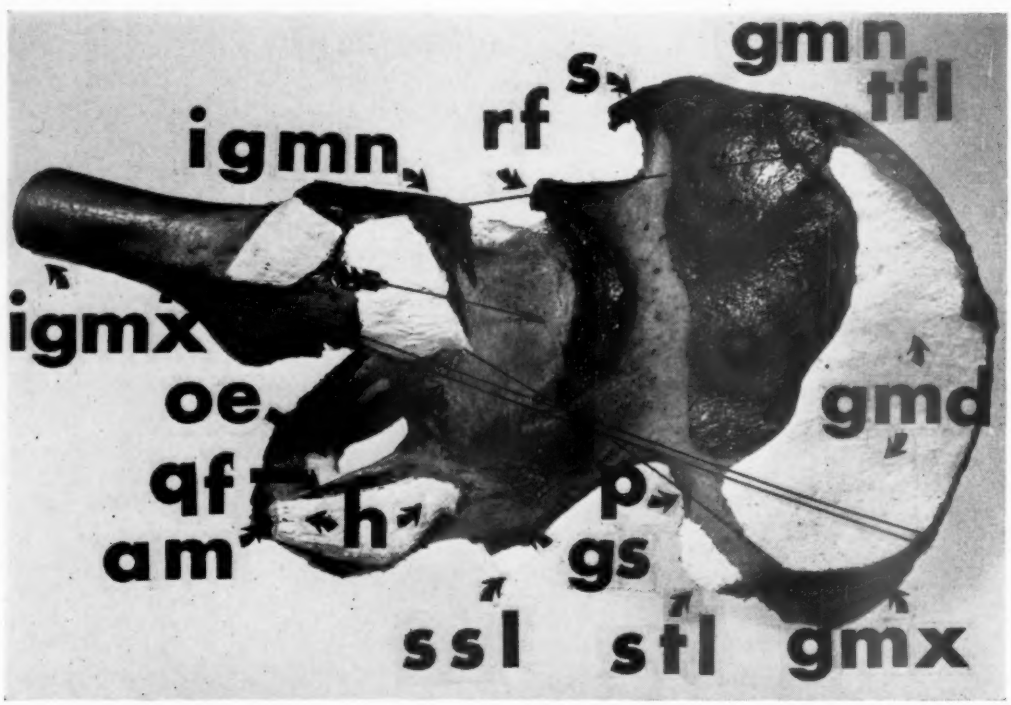


Fig. 1.—Lateral view of left hip with needle in joint cavity. By medial rotation the greater trochanter has been brought out from under the anterior margin of gluteus maximus (double line), and the neck and shaft of the femur are in line. The needle reaches the joint capsule by passing through gluteus medius (margins indicated by narrow lines) and either gluteus minimus or piriformis. Key: am = origin of adductor magnus, gmd = origin of gluteus medius, gmn = origin of gluteus minimus, gmx = origin of gluteus maximus, gs = origin of gamellus superior, h = origin of hamstrings (simimembranosus, semitendinosus, and long head of biceps), igmn = insertion of gluteus minimus, igmx = insertion of gluteus maximus, oe = origin of obturator externus, p = origin of piriformis, qf = origin of quadratus femoris, rf = origin of rectus femoris—both straight and reflected heads, s = origin of sartorius, stl = sacrotuberous ligament, ssl = sacrospinous ligament, tfl = origin of tensor fasciae latae.

terior approach (Henle[2] and Mawson[11]). In all but the anterior approach the greater trochanter serves as a landmark. After considering possible advantages and disadvantages of the various approaches, one essentially like that of Krause was selected.

The recommended approach utilizes medial rotation of the thigh to bring the greater trochanter out from under gluteus maximus and to bring the neck

of the femur into a plane parallel with the table. Then with the thumb and index finger delimiting the greater trochanter, the needle is inserted superior to the middle of the upper margin, parallel to the table, and at right angles to the femur. When so placed it will pass through gluteus medius, occasionally the posterior part of gluteus minimus, and will contact bone at a nonarticular surface, the junction of head and neck of the femur. Since at this point the capsule extends almost to the greater trochanter, injections made here will be intrasynovial. For intra-articular paracentesis the needle may be withdrawn somewhat and directed slightly superiorly to pass over the head of the femur (Figs. 1 and 2). This insertion should be made under fluoroscopic observation using Diodrast to make certain that the joint has been entered before aspiration or injection is attempted (Pruce, Miller, and Berger[16]).

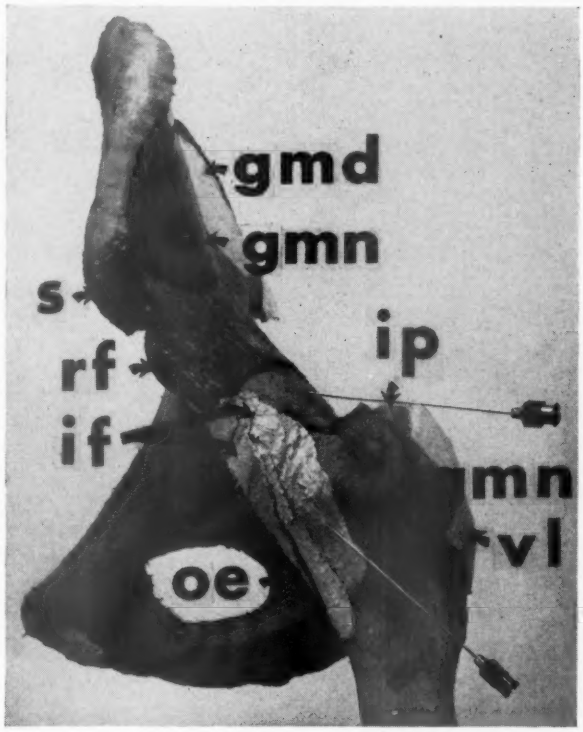


Fig. 2.—Anterior view of left hip showing angle of insertion of needle in joint cavity. A second needle has been inserted through the iliofemoral ligament (if) in the anterior part of the capsule according to the anterolateral approach of Landsmeer and Koumans.[10] Key: gmd = origin of gluteus medius, gmn = origin of gluteus minimus, if = iliofemoral ligament (Y-ligament), igmn = insertion of gluteus minimus, ip = insertion of piriformis, oe = origin of obturator externus, rf = origin of rectus femoris, s = origin of sartorius, vl = origin of vastus lateralis.

The following advantages of the lateral approach as outlined here may be enumerated:

1. This approach avoids large vessels and nerves. The largest vessels in the vicinity are the inferior branch of the superior gluteal artery and its accompanying vein. These cross the middle of the belly of gluteus minimus an inch or more superior to the path taken by the needle. In the region of the

needle path in the anterior approach are the superficial circumflex iliac vessels, lateral femoral cutaneous nerve, and, deeper, the lateral femoral circumflex artery and vein together with branches of the femoral nerve.

2. Because of great variations in size and even in proportions of parts, absolute measurements such as recommended by Hollander[5] (p. 13) can hardly be expected to result in reaching the same spot in a man who is six feet tall and in a woman who is a foot shorter. By contrast the uppermost border of the greater trochanter and the junction between head and neck of the femur lie in the same horizontal plane regardless of size and sex. Therefore, a needle passed above the greater trochanter and at right angles to the leg may be expected to enter the synovial cavity and strike the junction of head and neck with great regularity.

3. In cases in which exostoses have developed, successful injections are more probable if the needle is passed into the joint cavity under rather than through the bony excrescences. This is the case in the recommended approach.

4. Fluoroscopic views are more readily interpreted when the needle is parallel to the plane of the screen than when at an angle. For this reason our approach facilitates accurate fluoroscopic control of the injection.

Another approach, which might be called the anterolateral has been strongly recommended by Landsmeer and Koumans.[10] The needle enters anterior to the greater trochanter and is directed along the neck of the femur toward the middle of the inguinal ligament (Fig. 2). Since the synovial sac extends anteriorly as far as the intertrochanteric line, this approach permits a large margin for error both in direction and depth of insertion. It gives excellent results in the hands of the authors mentioned above; however, Hollander,[5] using essentially similar injection, finds that this "is also difficult" (p. 13). Since the nearest bony landmark, the tip of the greater trochanter, lies both superior and lateral to the cutaneous entrance point for the needle, it is thought that fewer difficulties will be encountered by the average physician if the approach recommended above is employed.

B. *The Knee (Humeroradial Articulation).*—The knee is the easiest joint of all to enter. Supra- and infrapatellar approaches each have adherents. In addition, Hollander[3-5] and Sperling[20] recommend a parapatellar approach. With failures of 7 and 0.6 per cent, respectively, it is obvious that little improvement is possible in the hands of experts. However, before recommending an approach for the average practitioner, one should make certain that it is not only simple and sure, but has the fewest potential disadvantages. The suprapatellar approach has the following disadvantages:

1. The suprapatellar bursa is not always continuous with that of the joint cavity. This is especially likely in the multilocular joints of patients with arthritis.

2. If there is no effusion, this bursa may be little more than a potential space.

3. It is markedly irregular in arthritics with hypertrophic synovias. In spite of its disadvantages the suprapatellar approach is preferred by some (Kling,[8] p. 257) because there is no hazard to articular surfaces by this technique. In describing the parapatellar injection Hollander[5] states that "the needle tip may crepitate on the under surface of the patella" (p. 9). He lists among advantages of this approach "the feel of the needle tip against cartilage is distinctive." For reasons stated earlier, contact of the needle tip with articular cartilage is considered undesirable by us rather than an advantage. The infrapatellar approaches which have been recommended in the past also involve some hazard to articular cartilages.

By contrast, the approach to the knee currently used by Dr. Paul L. Reith* appears to combine advantages of the other approaches and involve few

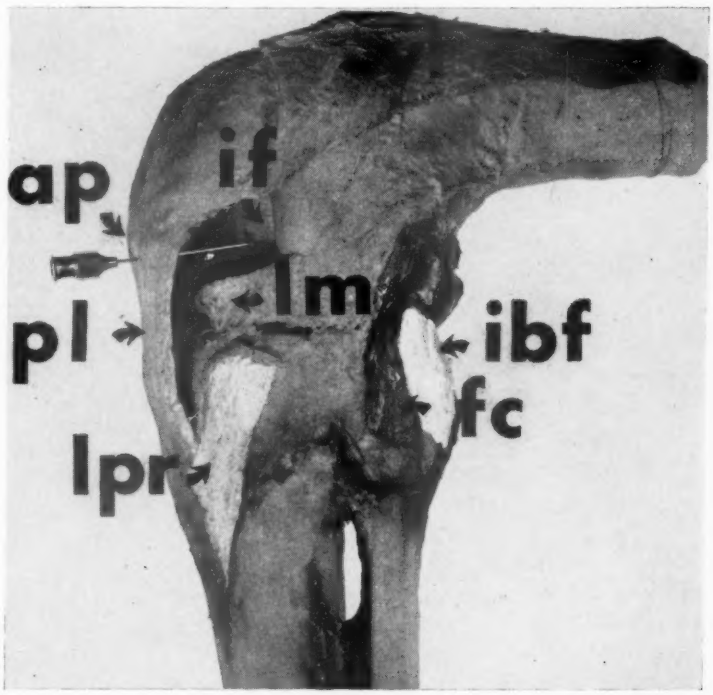


Fig. 3.—Lateral view of left knee with needle in joint cavity. The tendon of insertion of vastus lateralis (vl) has been incised and reflected to show the interior of the joint cavity. The needle was passed through the patellar ligament (pl) immediately inferior to the apex of the patella (ap) and points toward the intercondylar fossa (if). Key: ap = apex of patella, fc = fibular collateral ligament, ibf = insertion of biceps femoris, if = intercondylar fossa, lm = lateral meniscus, pl = patellar ligament, vl = vastus lateralis (incised and reflected anteriorly).

if any disadvantages. With the knee flexed 90 degrees, the needle is inserted immediately below the apex of the patella through the middle of the patellar ligament (Figs. 3 and 4). It passes through the fat pad and into the intercondylar fossa. Since it is above the middle of the fossa, it is superior to the anterior cruciate ligament and will not encounter the posterior cruciate ligament unless the needle passes almost through the articulation. This event can be prevented by avoiding the use of an excessively long needle.

*I wish to acknowledge valuable suggestions from Dr. Reith in all phases of this study.

An anatomic study shows that this approach to the knee satisfies the criteria for a good injection site. It has a palpable bony landmark immediately superior to the injection site. There are no large vessels or nerves which might be penetrated. Because of the shape of the femoral condyles, flexion greatly enlarges the vertical dimensions of the joint cavity. Flexion also stretches the patellar ligament. Finally, the probability of scoring the articular surfaces is reduced to the vanishing point since the tunnel between the condyles into which the needle is inserted provides a large margin for error (a circle about ¾ inch in diameter).

Since there are very few pain fibers in the patellar ligament, this approach has the added advantage of being relatively painless.

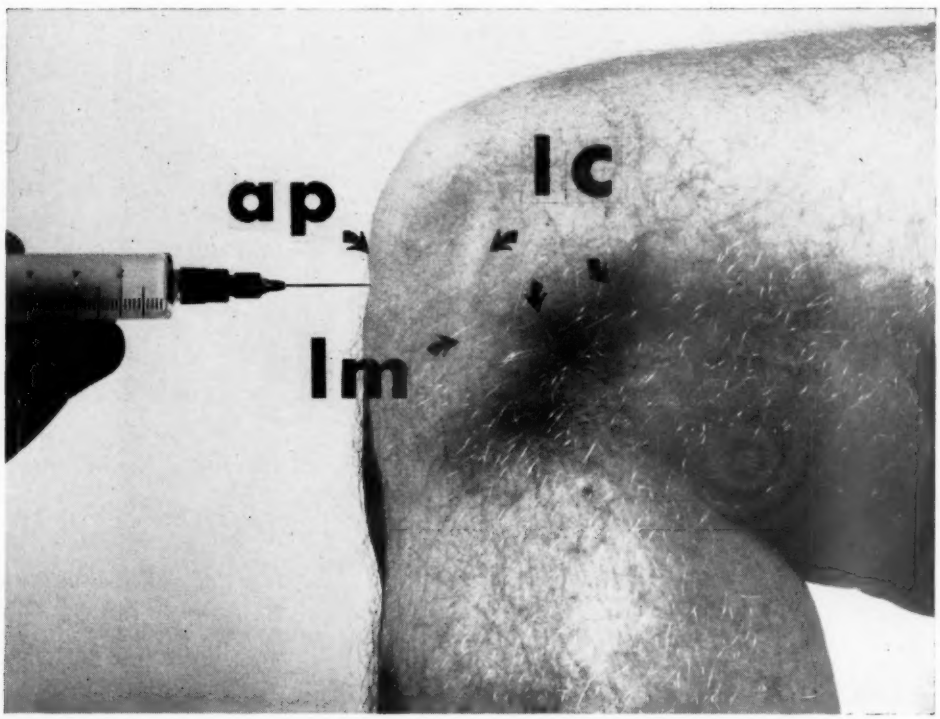


Fig. 4.—Lateral view of left knee illustrating site for paracentesis. With the knee flexed 90 degrees, the needle is inserted through the patellar tendon immediately inferior to the apex of the patella (ap). Key: ap = apex of patella, lc = lateral condyle of femur, lm = lateral meniscus.

C. *The Ankle (Tibiotarsal Articulation).*—As is true in its homologue the wrist, the chief nerves, blood vessels, and tendons of the foot pass along the flexor (= plantar) surface. In addition, the plantar surface contains 10 intrinsic muscles and an extremely tough weight-bearing fascia as contrasted with the single extensor digitorum brevis with its 4 bellies on the dorsum. As a consequence the dorsum provides the most favorable sites for paracentesis of the entire series of joints which are located in the ankle and foot.

Superficial structures of importance which cross the dorsum of the ankle are, from medial to lateral, the saphenous nerve, the great saphenous vein overlying the medial malleolus, the superficial peroneal (fibular) nerve, and

lesser saphenous vein. The latter reaches the dorsum by passing posterior to the lateral malleolus. Deeper structures from medial to lateral are tibialis anterior, extensor hallucis longus, deep peroneal nerve, the dorsalis pedis artery and vein, the extensor digitorum longus tendons, peroneus tertius (when present), and the anterior fibular malleolar artery and accompanying vein.

The ankle joint may be approached from either anteromedial or anterolateral directions with very little choice between the two approaches. The anteromedial was selected because there is slightly more space for insertion of the needle between the joint surfaces when the foot is plantar flexed.

Fig. 5.—Dorsomedial view of left foot showing site for paracentesis of ankle. The index finger is palpating the medial malleolar sulcus, medial to the tendon of tibialis anterior (ta). Note that the tendon of extensor hallucis longus (ehl) is lateral to that of tibialis anterior. Key: ehl = tendon of extensor hallucis longus, mm = medial malleolus, ta = tendon of tibialis anterior.

1. *Anteromedial approach:* (Figs. 5, 6, 7, and 8). This approach is similar to those of Hollander and Sperling although utilizing different landmarks. The chief bony landmark selected was the medial malleolar sulcus (the notch between the medial malleolus and the inferior articular surface of the tibia). With the foot in plantar flexion this sharp angle of bone can be palpated medial to the tendon of tibialis anterior. It and the more laterally placed tendon of extensor hallucis longus can be readily distinguished if the subject inverts the foot to tense tibialis anterior and then alternately flexes and extends the great toe. The differentiation is not quite as easily made with the plantar flexed as with the dorsiflexed foot. This perhaps explains why both

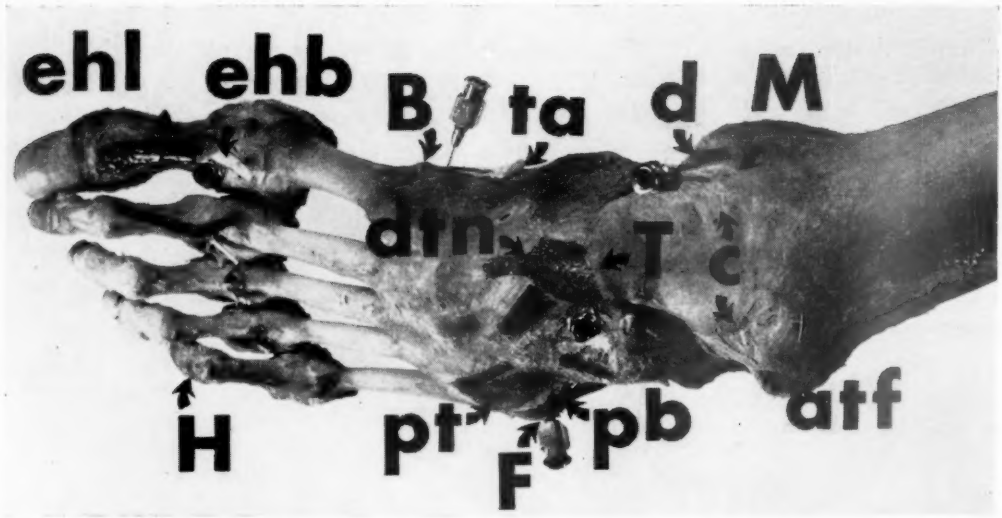


Fig. 6.—Dorsal view of left foot with needles in five joints. Needles are shown in the tibiotalar articulation, the talonavicular, the first and fifth tarsometatarsal and first metatarsophalangeal joints. The bony landmark for the talotibial joint is the medial malleolar sulcus (M). That for the talonavicular is the head of the talus (T). The landmark for the first tarsometatarsal joint is the base of the first metatarsal (B); that for the fifth is the tubercle of the fifth metatarsal (F). For the metatarsophalangeal and interphalangeal joints the head of the more proximal bone (H) is a readily palpable landmark with the joint flexed (the side view, Fig. 7). Key: bony landmarks—B = base of first metatarsal, H = head of phalanx, T = head of talus, M = medial malleolar sulcus, F = tubercle of fifth metatarsal; other structures—atf = anterior talofibular ligament, c = capsule of talotibial joint, d = deltoid ligament, dtn = dorsal talonavicular ligament, ehb = tendon of extensor hallucis brevis, ehl = tendon of extensor hallucis longus, pb = tendon of peroneus brevis, pt = insertion of peroneus tertius, ta = tendon of insertion of tibialis anterior.

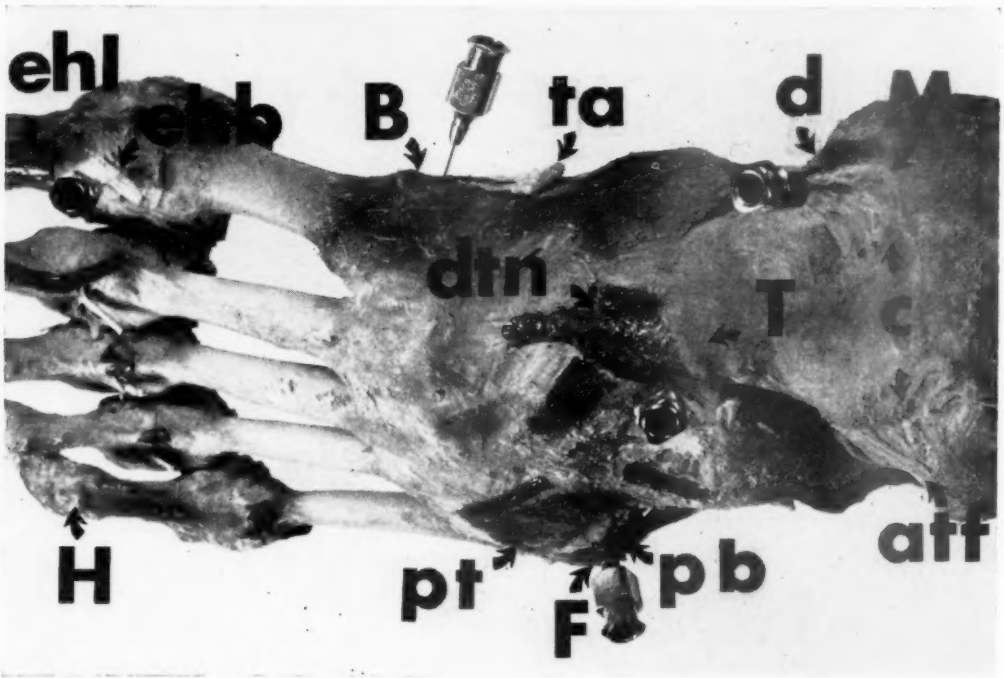


Fig. 7.—Enlarged view of dorsum of left foot with needles in five joints. For description and key to labels see Fig. 6.

Hollander and Sperling say to insert the needle medial to extensor hallucis longus instead of tibialis anterior. The lateral side of extensor hallucis longus is definitely to be avoided since the deep peroneal nerve and dorsalis pedis artery and vein are located here.

With the foot plantar flexed the talar trochlea usually can be palpated. The needle is directed between this and the lateral surface of the medial malleolus. Since the trochlea is wider anteriorly than posteriorly, plantar flexion opens the joint mortise providing more space for insertion of the needle (Fig. 7). It also tenses the joint capsule and the deltoid ligament.

2. *Anterolateral approach:* The bony landmarks recommended for this approach are the medial margin of the lateral malleolus and the lateral prominence of the trochlea tali. After the long extensors of the toes (and when present peroneus tertius) are identified, the needle may be inserted into the angle formed by the medial (articular) surface of the lateral malleolus and the lateral part of the distal end of the tibia. Plantar flexion both tenses the capsule and opens up the joint mortise for this as well as for the anteromedial approach.

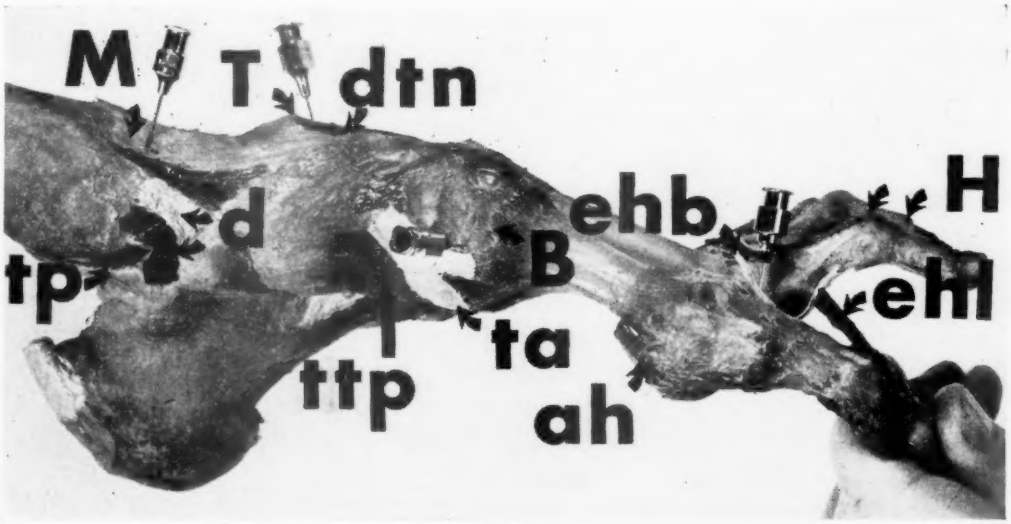


Fig. 8.—Medial view of foot showing needles in four joints. This view shows the relationship of the needle in the talotibial joint to the deltoid ligament (d) as well as to the medial malleolar sulcus (M). The site and bony landmark (T) for talonavicular paracentesis is well shown in this view. The relationship of the insertion of tibialis anterior (ta) to the needle in the first tarsometatarsal joint is also clearly indicated. This view also emphasizes the fact that the joint cavities of the metatarsophalangeal joints and of the interphalangeal joints are distal to the head (H) of the more proximal bone. Note also the plantar flexion of the foot. This increases the dorsal extent of the joint cavities and places the dorsal part of the joint capsules on stretch. Key: bony landmarks—B = base of first metatarsal, H = head of phalanx, T = head of talus, M = medial malleolar sulcus; other structures—ah = tendon of insertion of abductor hallucis, d = deltoid ligament with its three parts, dtn = dorsal talonavicular ligament, ehb = tendon of extensor hallucis brevis, ehl = tendon of extensor hallucis longus, ta = tendon of insertion of tibialis anterior, tp = groove for tendon of tibialis posterior, ttp = tendon of tibialis posterior.

D. *Intertarsal Articulations.*—Since most of the intertarsal articulations present no palpable bony landmarks, the only comment which will be made here is that they should be approached from the dorsal side. Hollander[5] recommends fluoroscopic guidance for all of these. However, since the head

of the talus usually is palpable, paracentesis of the talonavicular joint is feasible without roentgenographic assistance. With the foot inverted and dorsiflexed and with the toes extended, the head of the talus is palpated between the tibialis anterior and extensor hallucis longus tendons. Then, with the foot plantar flexed to open the space between the talus and navicular, the needle is inserted at right angles to the surface, immediately distal to the sharp margin of the head of the talus and medial to extensor hallucis longus (Fig. 7).

E. *Tarsometatarsal Articulations.*—Among these joints only the first and fifth are readily accessible. The first is easily located by tracing the tendon of tibialis anterior to its insertion on the medial inferior surface of the first cuneiform and first metatarsal distal and proximal to the joint (ta, Fig. 7). This tendon is readily palpated if the patient is required to elevate the foot against resistance. The needle may be inserted immediately proximal to the base of the first metatarsal. This produces a palpable projection on the medial aspect of the longitudinal arch of the foot (Figs. 5, 6, and 7).

The fifth tarsometatarsal joint is the more prominent of the two because of the large tubercle at the base of the fifth metatarsal for the insertion of peroneus brevis (pb, Figs. 5 and 6). A needle placed immediately above the insertion of the muscle and proximal to the tubercle will find the joint cavity (Fig. 6).

F. *The Toes.*—The fundamental arrangement of structures in the toes is the same as that of the fingers with extensor tendons dorsal, nerve and vascular supply on the medial and lateral sides, and flexor muscles and tendons on the plantar surface. All of these joints follow the general rule that joints are best approached from the extensor surface. Paracentesis of the metatarsophalangeal and interphalangeal articulations is best approached from the dorsum, either medial or lateral to the extensor tendons (Figs. 5, 6, and 7). The tendons may be visualized first by having the patient contract the extensors of the toes. Then, as in the case of the fingers, the dorsal part of the joint cavity can be enlarged somewhat by a combination of distraction and passive flexion of the digit. In cases with little or no swelling the injection site is then seen as a depression which appears on either side of the extensor during distraction.

## DISCUSSION

The fundamental simplicity of joint paracentesis and its applicability to office practice has already been emphasized with respect to the superior extremity (Miller[12]). With the exception of the hip joint, paracentesis of the joints of the inferior extremity is no more difficult than of the superior extremity. The procedures can be mastered in a short time by anyone who will review the anatomy of the regions in question.

The hip joint presents some special problems. Injections here have the highest chances of failure (Hollander and associates).[7] The difficulties encountered in paracentesis of this joint derive chiefly from the tight fit of its component parts and its distance from the surface. As compared with the

approach suggested here, the commonly employed techniques utilize one or more of the following: (1) somewhat more remote landmarks, (2) estimations of angles, and (3) arbitrary distances. Since each of the aforementioned procedures tends to introduce errors, it may be anticipated that when a series as extensive as that of Hollander has been accumulated using the lateral approach, the percentage of failures may be less than appears in the current figures (Table I).

TABLE I. COMPARISON OF RECOMMENDED APPROACHES AND THOSE EMPLOYED BY A GROUP REPORTING 10,197 INJECTIONS OF CORTISONE*

| | RECOMMENDED APPROACHES | HOLLLANDER ET AL.[7] | | |
|---|---|---|---|---|
| | | APPROACHES | NUMBER INJECTED | PER CENT FAILURES |
| Hip | Lateral—superior to greater trochanter | Anterior | 453 | 54 |
| Knee | Anterior—intrapatellar | Medial—parapatellar | 6,828 | 7 |
| Ankle | Anteromedial—lateral to medial malleolar sulcus, medial to tibialis anterior | Anteromedial—medial to extensor hallucis longus | 561 | 16 |
| All other joints | | Various | 119 | 37 |

*Data from Holland and his co-workers.[7]

The recently described anterolateral approach of Landsmeer and Koumans[10] has many of the advantages of the recommended approach and in their hands gives very satisfactory results. However, since the entrance point for the needle has no immediately adjacent bony landmark, their technique might not give as good results in the hands of the general practitioner as one recommended here.

The knee has the distinction of being both the easiest joint to enter and the most frequently injected joint (Table I). With a failure rate of only 7 per cent the opportunities for improvement by using another approach are limited. However, since nearly 70 per cent of all joint injections are into the knee, even a small percentagewise increase in successes will mean an appreciable decrease in the total number of failures. More important, however, is the fact that with our technique the needle is inserted into the intercondylar tunnel and thus completely avoids contact with articular cartilage. Since repeated injections of the knee are common, the possibility of repeated scoring of the articular cartilages becomes an important consideration in the selection of the injection site.

The differences between Hollander's and Sperling's approaches to the ankle joint (tibiotalar) and that recommended here involve chiefly the use, on the medial side, of an adjacent bony landmark instead of a measurement and the palpation of the tendon of tibialis anterior rather than extensor hallucis longus (Hollander,[4, 5] Sharp and Dohme,[18] and Sperling[20]). Since the former lies medial to the latter along its entire course and, therefore, is closer to the selected injection site, the rationale for its use is obvious. With

the addition of strong plantar flexion of the foot to open the joint mortise anteriorly, it is possible that the incidence of failures in this injection may be reduced below 16 per cent (Table I).

There are no detailed reports of the results of any extensive series of injections of the small joints of the inferior extremity. They are included in Table I under the heading, "All other joints." However, since they are covered only by skin, penetration of the synovial cavity from either dorsolateral or dorsomedial direction presents no great problems.

It is hoped that this study, the preceding one on the superior extremity (Miller[21]), and the one that follows which gives specific directions as to the techniques for the more commonly injected joints (Pruce, Miller, and Berger[16]) will encourage a more extensive use of paracentesis not only for hormone therapy but also for diagnostic purposes. With an adequate knowledge of the pertinent anatomy and reasonable care, very few joints indeed are resistant to penetration by a needle.

These studies are also germaine to the use of hypospray for intra-articular injection (Ziff, Contreras, and Schmid[21]) since accurate localization of the joint cavity is equally important in this method of injection as in the more usual techniques.

## SUMMARY

From an anatomic study of the joints of the inferior extremity the following sites were selected for joint paracentesis:

1. For the hip: a lateral approach immediately superior to the middle of the greater trochanter with the leg adducted and medially rotated slightly.
2. For the knee: an anterior approach immediately inferior to the apex of the patella with the knee flexed to 90 degrees.
3. For the talotibial joint: an anterior approach immediately inferior to the medial malleolar sulcus, with the foot plantar flexed.
4. For the talonavicular joint: a dorsal approach immediately distal to the talar head, with the foot plantar flexed.
5. For the first tarsometatarsal joint: a medial approach immediately proximal to the base of the first metatarsal.
6. For the fifth tarsometatarsal joint: a lateral approach immediately proximal to the tubercle and dorsal to the peroneus brevis tendon.
7. For the metatarsophalangeal joints and the interphalangeal joints: a dorsal approach distal to the head of the more proximal bone either medial or lateral to the extensor tendons and aided by flexion and distraction of the digit.

The merits of these approaches are discussed in relation to those of others.

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# A FURTHER INVESTIGATION OF THE SURGICAL APPLICATION OF TITANIUM METAL IN DOGS

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PREVIOUS investigation has demonstrated that titanium metal is inert in the body of a dog.[1] Various physical forms of this metal are being used as implants in this animal to explore the use of this metal as an adjunct to surgery. These include a fracture plate, nuts, bolts, screws, pins, and a skull plate.

## METHODS AND EQUIPMENT

In this study, the procedure was as follows. Under surgical asepsis the right femur of a dog was fractured (Fig. 1). A custom-made fracture plate of titanium, 3¼ inches in length, ½ inch in width, and 1/16 inch in thickness, with custom-made bolts of $\frac{3}{32}$ inch diameter and corresponding custom-made nuts (Fig. 2), were then used for fixation of the reduced fracture (Fig. 3). The plate remained in situ for 120 days, with the dog being allowed complete freedom of use of his limb. The progress of healing and callus formation were observed periodically by means of radiographs (Figs. 4 and 5). The plate, with an adequate amount of bone, was then surgically removed from the animal. The bone was separated from the plate and nuts and bolts and fixed for microscopic study of the fracture site.

Into the right femur of another dog, custom-made screws and pins were placed under surgical asepsis (Fig. 6). These remained in situ for 180 days. The tolerance to the titanium by the bone and the surrounding tissue was checked at intervals radiographically. This and gross examination revealed an acceptance of the metal by the tissue.

In 2 dogs the left side of the skull was trephined to the dimensions of 1 times $1\frac{3}{16}$ inches. A skull plate whose dimensions are $1\frac{3}{16} \times 1\frac{3}{8} \times \frac{5}{1000}$ inches was positioned over this opening in the skull and was secured by turning down a $\frac{5}{32}$ inch flange at 4 opposing points to prevent the plate from moving laterally. It was held in position by the scalp. (Fig. 7.)

## RESULTS

Objectively, the dog in each case demonstrated a normal convalescence—at first favoring the operated leg, and then re-establishing its function. The dog with the skull plate retained all its functions. There were no signs of infection or inflammation.

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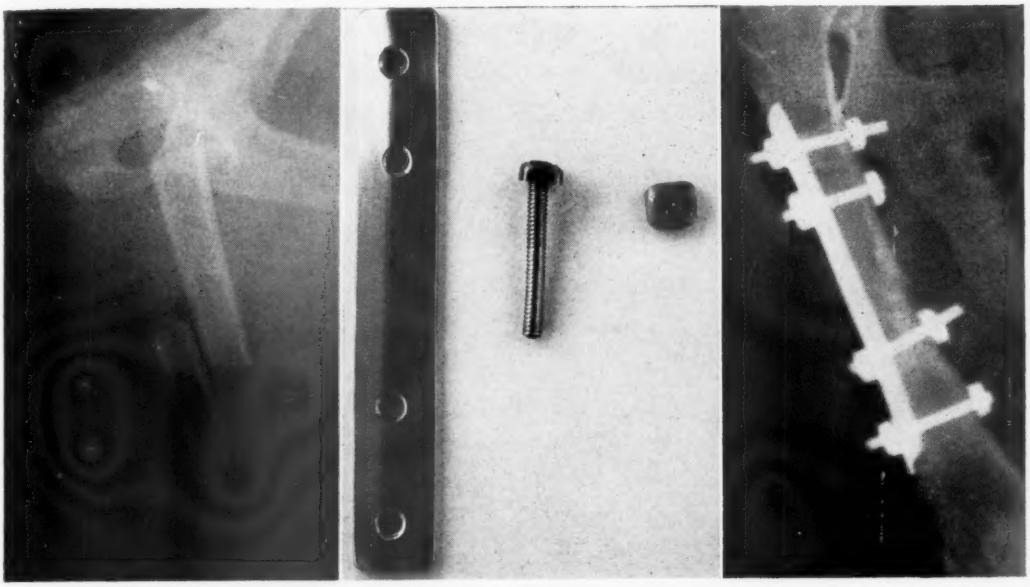

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Radiograph of right femur of dog with surgical fracture.

Fig. 2.—Custom-made fracture plate of titanium with custom-made titanium bolt and nut.

Fig. 3.—Radiograph of right femur of dog with surgical fracture reduced and immobilized with titanium fracture splint.

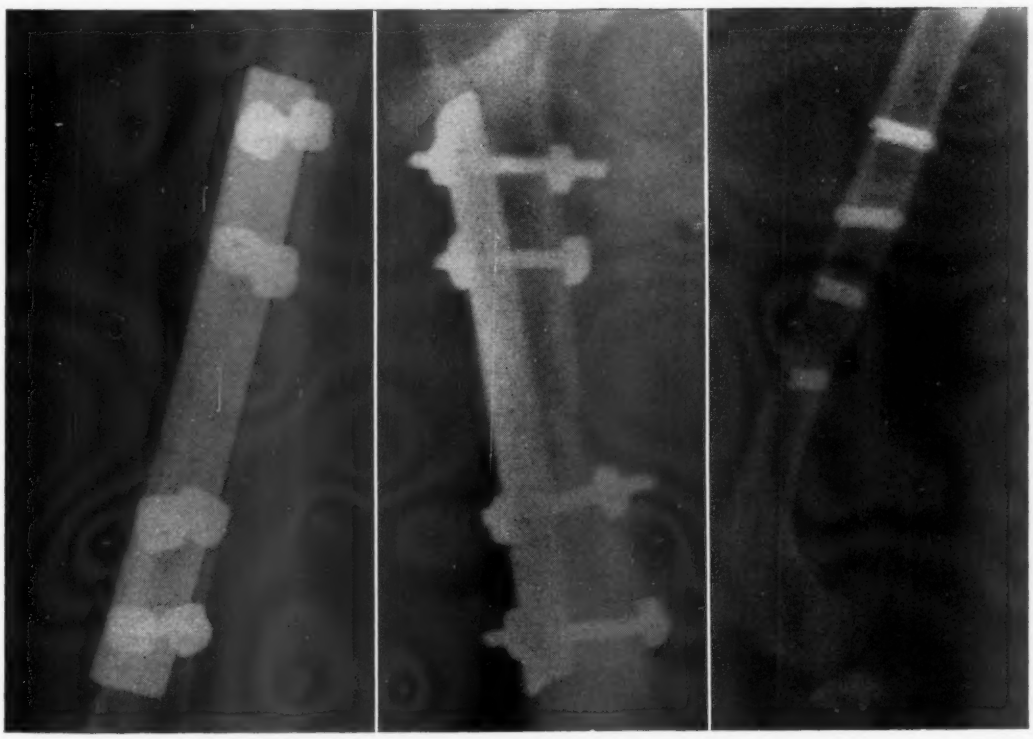

Fig. 4. Fig. 5. Fig. 6.

Fig. 4.—Radiograph of right femur of dog with immobilized fracture, showing callus formation.

Fig. 5.—Radiograph of right femur of dog with healed fracture.

Fig. 6.—Radiograph of right femur of dog with placed titanium screws.

Radiographic findings were as follows. The fractured femur that had been reduced and immobilized by the titanium plate showed gradual increased callus formation and healing of the fracture. There was no evidence of osteolytic activity around the bolts or nuts in or on the bone and no tissue reaction to their extraosteal portions. An interesting finding in the case of the skull plate was that the titanium sheet was radiolucent (Fig. 7).

Fig. 7.—Radiograph of dog with titanium skull plate placed on left side of skull.

## DISCUSSION AND CONCLUSIONS

Evidence has been provided by this investigation that various implant forms of titanium are well tolerated by dogs. These forms were used as adjuncts to surgery in circumstances similar to those in which stainless steel and tantalum have served. Their application in definitive surgery has been demonstrated. The lack of tissue reaction to this metal, its abundance in nature, and its relative low cost as compared with the metals now being used clinically are definite advantages. It is a comparatively light metal, being 40 per cent lighter than stainless steel and 75 per cent lighter than tantalum, and yet its tensile strength is equal to or better than that of these metals.

The fact that titanium in the thickness used for the fabrication of a skull plate is of adequate strength and is radiolucent permits unhampered radiographic evaluation of surrounding and underlying tissues.

SUMMARY

This report is based on the study of the tolerance of the tissue of dogs to implants of titanium adjunctive appliances inserted under aseptic surgical conditions. These implants remained in situ for several months. The titanium remained inert and aided in the definitive treatment indicated.

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# Editorial

CONDUCTED BY I. S. RAVDIN, M.D.

## The Mechanism by Which Ingested Fat Delays Gastric Emptying

IN A RECENTLY published article,[7] treatment of the postgastrectomy dumping syndrome by a high fat diet was reported. In seven cases, marked symptomatic improvement and progressive weight gain occurred. In developing the theoretical basis for the dietary treatment of this disturbance the antrum of the stomach is implicated in a fashion which, we believe, is not in accord with currently accepted physiologic facts and clinical observations. As stated, the dumping syndrome is much less frequent after gastroenterostomy alone. Although the incidence may be somewhat less, the syndrome is certainly still very common following this procedure. The frequency of the syndrome's occurrence is said to be unrelated to the type of reconstitution of gastroenteric continuity. Many authors,[1, 7, 9, 11, 12, 13, 15] however, report rather convincing evidence that it is less frequent after gastroduodenal rather than gastrojejunal anastomosis.

The statement is made that after the pyloric antrum and proximal duodenum are removed, delay in gastric emptying because of the presence of fat is no longer observed, but that this is not true if a simple gastroenterostomy is performed. The reference for this statement is a paper published in 1952 by Waddell and Wang.[17] These authors studied the rate of gastric evacuation in human subjects by mixing an emulsified fat (Lipomul) with barium sulfate. The per cent gastric residue was estimated from fluoroscopic examination at hourly intervals for four hours. Ten normal subjects all showed retention of barium (trace to 80 per cent) at four hours. Ten patients with partial gastrectomy and gastrojejunostomy showed complete emptying of the gastric remnant in less than one hour in nearly all cases. Five patients with gastroduodenostomy following partial gastrectomy showed the same rapid emptying. In two patients with gastrojejunostomy alone, however, there was still 10 per cent gastric residue after three hours.

The original observation that fat inhibits gastric emptying was made by Ewald and Boas[2] in 1886. In elucidating the mechanism of this effect, Farrell and Ivy[3] showed that, in a dog with a completely denervated fundic pouch, ingested olive oil caused inhibition of the motor activity of the pouch. The hormone transmitting this effect was named "enterogastrone" by Kosaka and Lim.[10] Enterogastrone inhibits the secretion of acid gastric juice as well as the motility of the stomach. Although apparently a potent physiologic mechanism, enterogastrone has not proved to be of value in the therapy of peptic ulcer.

Prior to these findings the idea prevailed that fat delayed gastric emptying by causing the pyloric sphincter to close. It has been established[14, 16] that fat slows gastric emptying by inhibition of contractions of the entire stomach including the pyloric sphincter. The emptying of the stomach contents is delayed because of decrease in the propulsive force.

It was found in Pavlov's laboratory[8] that fat confined to the stomach failed to produce depression of gastric activity. Subsequent work demonstrated that enterogastrone is released by contact of fat, and to some extent of carbohydrate, with the mucous membrane of the entire proximal small intestine, including the duodenum and the first portion of jejunum.[4, 5] Thus, enterogastrone is not released by contact of fat with the antral mucous membrane. We studied the physiology of the antrum using dogs prepared with isolated pouches of the antrum.[18] In this preparation the proximal portion of the duodenum was used as a conduit to create a cutaneous fistulous opening into the antrum. We found that perfusion of such an antral pouch had no effect whatever on motility in the animal's main stomach; also fat strongly inhibited gastric motility in antrectomized dogs.[6] In patients with partial gastrectomy, ingested fat inhibited motility of the gastric remnant equally well with gastrojejunal and gastroduodenal reconstruction.[6]

These findings are at variance with those reported by Waddell and Wang.[17] These authors, however, reported only two patients with gastrojejunostomy alone. It seems likely that in these patients the gastrojejunal anastomosis was improperly placed, partially stenosed from marginal ulcer, or, for some other reason, not adequately functioning. Certainly the delay in gastric emptying reported cannot be attributed to the action of fat on the antrum.

We believe that treatment of the postgastrectomy dumping syndrome with a high fat diet is highly desirable because of the high caloric content of such a diet and the reduced amount of highly hydrolizable substances. Nonetheless, we wish to point out that excision of the gastric antrum is not per se responsible for the development of the dumping syndrome, but that this is dependent upon the creation of a relatively large sphincterless neostoma between the stomach and small intestine. Furthermore, the inhibitory effect of fat on gastric motility is mediated not through the antrum but through the duodenum and upper jejunum by release of the hormone, enterogastrone.

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## Erratum

The editorial entitled "The Stethoscope—Historical Instrument?" by Joseph R. Wilder of the New York Medical College, which appeared in the May issue of the JOURNAL, page 842, erroneously gave the writer's address as Baltimore, Md. Dr. Wilder's name should be followed by New York, N. Y.

# Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

## PANCREATICOJEJUNOSTOMY FOR CHRONIC PANCREATITIS

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THE etiology of recurrent pancreatic inflammatory disease remains an enigma. Since nonoperative treatment cannot control the disease, the operative approach selected assumes great importance. The procedures usually recommended can be divided into 2 main groups: those directed at suspected causes[4, 11, 24] and those directed at relief of symptoms.[7, 23, 25, 30] However, improper matching of operation to patient often leads to inconstant results. In 1953, the following program of study was started in New York. It was undertaken in order to evaluate the clinical results of a single method of surgical management as applied to a group of carefully selected patients. Since January, 1957, the program has included case material from the University of Oklahoma Medical Center. By rigid criteria of postoperative evaluation over a period of 3 years, 80 per cent of these patients showed dramatic improvement.

### RATIONALE OF TREATMENT

Berens,[3] utilizing autopsy material, observed a high incidence of obstruction of the pancreatic ducts with dilatation of the ductal system proximal to the obstruction. This has been confirmed by DuVal.[18] Additional evidence of pancreatic duct obstruction has been contributed by Leger,[22] Appelby,[1] and Gillette.[21] Edmundson[19] demonstrated, in the chronically diseased pancreas, that calcifications occurred in epithelial-lined cavities in communication with the obstructed ductal system.

The purpose of the following study was, first, to assess the accuracy of preoperative detection of incomplete pancreatic duct obstruction in patients; and, second, to assay the effect of decompression of the obstructed pancreatic duct in patients with chronic pancreatitis.

### SELECTION OF PATIENTS

Only patients with a long history of severe episodes of abdominal pain, interference with nutrition, weight loss, floating stools, and personality disorders were selected. Many of these patients had pancreatic calcification, alcoholic histories, diabetes, and narcotic addiction. None of them had pancreatitis in association with biliary tract disease,[20, 26] ulcerative colitis,[2] mumps,[5] coronary thrombosis,[6] circulatory failure,[27] trauma,[28] or surgical operation.[13]

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The hospital evaluation was identical in all cases. It included a complete history, physical examination, chest x-ray, red and white blood cell count, hemoglobin, analysis of the urine for sugar and albumin, blood urea nitrogen, plasma protein, glucose tolerance test, and initial and interval measurement of serum amylase. All patients underwent fluoroscopic examination of the stomach and duodenum with barium, and oral cholecystography with telepaque. A secretin test by the technique of Dreiling[12] was done when commercial secretin was available.

These data were reviewed in each patient, and the status of the disease process evaluated. Using the criteria below, the likelihood of pancreatic duct obstruction was assessed and the patients were subjected to exploration and decompression of the pancreatic duct.

*Pain.*—Every patient in the series complained of periodic episodes of violent pain, usually epigastric in location. Back or flank pain was more prominent in some individuals. Early in the disease, freedom from pain between attacks was a consistent finding. With progression, however, many patients observed the pain to become more constant.

*Duration of Symptoms.*—All patients selected had had symptoms for 4 years or longer, unless there was other evidence of chronicity such as calcification, marked weight loss, drug addiction, or severe personality derangement. Eight patients were included in the latter category.

*Weight Loss.*—Ten pounds (4.5 Kg.) or more were lost by all but one patient who denied weight loss, but was included because of a 5-year history of pain with jaundice, alcoholism, and a series of 3 previous abdominal operations in which pancreatic disease had been described.

*Floating Stools.*—This finding was helpful, when present, as an indication of pancreatic destruction.

*Pancreatic Calcification.*—This was invariably significant when an adequate history was available.

*Diabetes.*—This was considered further supportive evidence of chronicity, with a long history or with pancreatic calcification.

*Secretin Test.*—Using the technique of Dreiling,[12] the duodenum was intubated with a Diamond[10] tube after a 12-hour fast. After ascertaining the position of the tube by fluoroscopy, Secretin* was administered intravenously (10 units per kilogram body weight). An 80-minute volume of duodenal aspirate was recorded in milliliters per kilogram body weight and analyzed for amylase content expressed in Somogyi units per kilogram body weight; 20-minute aliquots were analyzed for bicarbonate ion concentration. Failure to concentrate bicarbonate to 90 meq. per liter in at least one 20-minute specimen was found to be the most valuable indication of the presence of chronic pancreatitis. Depression of volume below 2.0 ml. per kilogram body weight was frequently observed and gave a positive correlation with the later finding of obstruction of the pancreatic duct. Enzyme studies gave little additional information and are not included here.

*Generously supplied by Eli Lilly and Company, Indianapolis, Ind.

*Oral Cholecystography.*—This was used only to eliminate the presence of disturbed function or pathology of the gall bladder.

*Gastrointestinal Barium Study.*—Again, this was used only to eliminate primary disease of the stomach or duodenum.

## OPERATIVE PROCEDURE

The technique of pancreaticojejunostomy has been described in detail elsewhere.[15] Cattell,[8, 9] Wangensteen,[29] and others have previously discussed the methods and value of decompression of the obstructed pancreatic duct. In this instance, preference for the principle of decompression via the tail of the pancreas, as outlined by DuVal,[14] is based solely on the ease of technical accomplishment as compared with an operative procedure directed at the head of the pancreas.

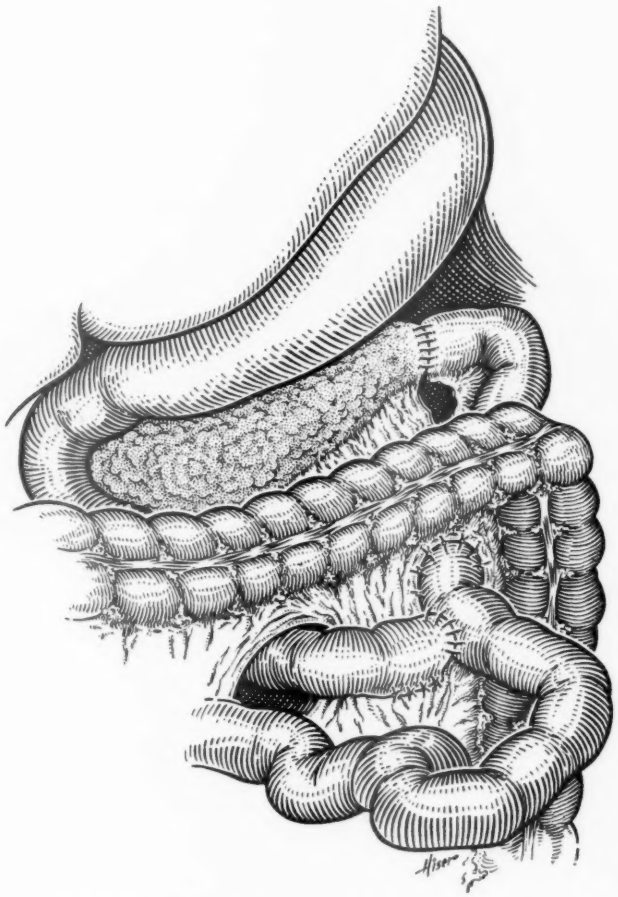

**Fig. 1.—Artist's sketch of the completed pancreaticojejunostomy.**

After careful abdominal exploration, the pancreatic duct was exposed by partial transection of the tail of the pancreas. The transverse diameter of the duct was measured, and its course through the body and tail was determined by insertion of a long, very flexible, olive-tipped probe (George P. Pilling

Co.); 70 per cent Diodrast was injected through a cannula, x-rays were taken of the ductal system, and ductal pressures were recorded when feasible. The latter studies will be reported separately.[16]

If an enlarged, dilated, or tortuous duct was encountered or if there was x-ray evidence of obstruction to flow of Diodrast into the duodenum, the tail of the pancreas and spleen were resected. The remaining pancreatic body and duct were anastomosed to the end of a 30 cm., retrocolic, Roux-Y limb of proximal jejunum. Intestinal continuity was re-established by end-to-side jejunojejunostomy near the ligament of Treitz. Calculi, when encountered, were removed if possible. The completed operative procedure is illustrated in Fig. 1.

All patients in the series were followed at frequent intervals after operation. The effects of the operation were evaluated in terms of freedom from pain, reversal of weight loss, change in demeanor, change in glucose tolerance, and drug addiction when applicable. Follow-up is short in some instances, but is complete on all patients for periods up to 42 months. The average interval since operation is now 15 months. Continued follow-up is planned for all patients.

## PATIENT FINDINGS

Twenty-six patients were selected and operated upon by the above methods and criteria. The accumulated data on these patients are summarized in Table I. The following observations and comments are pertinent.

*Duration of Symptoms.*—Varied from 1 to 10 years, with an average of 5 years. Among the patients with shorter histories, however, were other evidences of chronicity (weight loss, diabetes, and calcification).

*Alcoholic Habits.*—Most of the patients used alcoholic beverages to excess, and nearly half of the patients were or had been severely alcoholic.

*Nutritional Status.*—Ninety-six per cent of the patients had lost weight, usually without specific reference to change in appetite. The weight loss averaged 12 Kg., and was usually associated with a history of floating stools. Frank steatorrhea was not seen in any instance. There was a positive correlation between the degree of weight loss and the degree of pancreatic duct obstruction.

*Diabetes.*—Twenty-seven per cent of the patients were diabetic before operation. There was a positive correlation between the presence of diabetes and the duration of symptoms. In patients with diabetes, symptoms were present for 6½ years; for the nondiabetic, 4½ years. Six of the 7 diabetic patients had calcification of the pancreas.

*Calcification.*—Fourteen patients (54 per cent) had calcification of the pancreas. Six of these patients were diabetic and a seventh was border-line by glucose tolerance test. The average duration of symptoms was a year and a half longer among those with calcification than those without, although 3 patients had calcification with symptoms of only one year's duration.

*Serum Amylase.*—Of the patients in this series only 20 per cent had a significant elevation of serum amylase during the attack of pancreatitis which caused their present admission and election for study. Previous records and

data were available for 17 of these patients which showed that 76 per cent had had significant elevation of serum amylase earlier in the course of their disease.

*Jaundice.*—Seven patients (27 per cent) had a history of obstructive jaundice. The gall bladder had been removed earlier in 3. The other 4 had normal function of the gall bladder. Primary disease of the common duct was not evident in any patient. It is likely that the intrapancreatic portion of the common bile duct becomes obstructed by inflammation of the head of the pancreas in a significant proportion of cases.

*Previous Surgical Treatment.*—Among the group who had not undergone previous surgical attempts to control their pancreatitis, there were only 6 patients. Of the other 20 patients, a total of 44 operations had been performed. One of them had had 7 operative procedures. This indicates clearly the difficulties of surgical management. Among the 7 patients who had undergone previous cholecystectomy, 5 had removal of normal gall bladders, one was interpreted as noncalculus cholecystitis, and one had cholelithiasis. The common duct had been reported as normal in each instance. One-quarter of this group had had sphincterotomy.

## OPERATIVE FINDINGS

*Pancreatic Ducts.*—Previous dissections[17] of pancreatic ducts indicated that a normal pancreatic duct rarely exceeds 3 mm. in transverse diameter in the tail of the pancreas. In this series 77 per cent of the ducts exceeded 3 mm. Among the 6 ducts measuring less than 4 mm. in diameter, obstruction was demonstrable in 2 by x-ray; one was not tested. Of these patients one had recurrent pain within 2 months after operation; the other 2 apparently are well 8 and 14 months after operation, respectively. Lack of appreciation of the pressure of dye injection in the attempt to demonstrate incomplete obstruction may have been of importance in these cases.

*Pathology.*—In most instances, the pancreas was found to be fibrotic, shrunken, and hard. Fat necrosis, edema, hemorrhage, and other accepted manifestations of acute inflammation were singularly absent. Pseudocysts were present in a few instances. Considerable peripancreatic fibrosis was observed involving, in particular, the adjacent viscera such as the splenic flexure and the posterior wall of the stomach.

Microscopic study of the resected tail revealed a severe degree of interstitial fibrosis, destruction and replacement of the acinar parenchyma, mild to moderate lymphocytic infiltration, and stasis of secretion in dilated ductules. In retrospect, it is interesting to note that in 3 of the patients without a dilated major pancreatic duct, the degree of fibrosis was considerably less pronounced than in the group as a whole. In general, the islets of Langerhans were preserved, although reduced in number and isolated by the massive fibrosis.

## RESULTS

*Deaths.*—There were no operative deaths in this series. One patient, a 28-year-old woman, died 3 months after operation with diabetic acidosis

TABLE I. DATA ON 26 CASES OF CHRONIC RELAPSING

| NO. | CASE | HOSPITAL AND LABORATORY FINDINGS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AGE AND SEX | DURATION IN YEARS | ALCOHOLISM PAST OR NOW | WEIGHT LOSS (POUNDS) | FLOATING STOOLS | JAUNDICE PAST—NOW | DIABETES | CALCIFICATION | HIGHEST AMYLASE* PAST—CURRENT | |
| 1 | S. B. | 39M | 10 | + | 21 | + | 0 | + | + | @ | 160 |
| 2 | E. C. | 28M | 2 | + | 30 | + | 0 | 0 | 0 | 620 | 402 |
| 3 | M. C. | 41F | 4 | 0 | 20 | + | 0 | + | + | 396 | 182 |
| 4 | G. C. | 31M | 3 | + | 30 | + | 0 | 0 | 0 | 392 | 108 |
| 5 | E. C. | 35F | 6 | 0 | 15 | + | + | 0 | + | @ | 84 |
| 6 | J. C. | 40M | 1 | + | 15 | + | 0 | 0 | + | 261 | 73 |
| 7 | J. E. | 38M | 6 | + | 15 | + | 0 | 0 | 0 | @ | 218 |
| 8 | A. F. | 53M | 2 | + | 10 | 0 | 0 | 0 | 0 | 524 | 340 |
| 9 | R. G. | 44M | 4 | + | 25 | + | 0 | 0 | 0 | @ | 388 |
| 10 | R. H. | 44M | 8 | + | 40 | + | + | + | + | 600 | 112 |
| 11 | E. H. | 45M | 9 | + | 20 | + | 0 | + | + | @ | 299 |
| 12 | P. L. | 46M | 5 | + | 30 | + | 0 | 0 | + | 429 | 28 |
| 13 | W. L. | 52M | 2 | 0 | 30 | + | + | 0 | 0 | 624 | 82 |
| 14 | W. M. | 36M | 8 | + | 39 | + | 0 | 0 | + | 628 | 40 |
| 15 | Z. M. | 36F | 9 | + | 20 | + | + | 0 | + | 596 | @ |
| 16 | P. P. | 27F | 1 | + | 20 | + | 0 | 0 | 0 | @ | 143 |
| 17 | J. Q. | 39M | 5 | + | 0 | 0 | + | 0 | 0 | 250 | 80 |
| 18 | N. S. | 37M | 1 | + | 100 | + | 0 | + | + | @ | 414 |
| 19 | J. S. | 26M | 5 | + | 12 | + | 0 | 0 | 0 | 696 | 40 |
| 20 | K. S. | 36M | 4 | + | 30 | + | 0 | ? | + | 80 | 36 |
| 21 | A. S. | 32F | 8 | + | 30 | 0 | 0 | 0 | + | @ | 96 |
| 22 | A. T. | 31M | 7 | + | 25 | + | + | 0 | 0 | 2256 | 450 |
| 23 | B. W. | 33M | 1 | + | 35 | + | 0 | 0 | + | @ | 296 |
| 24 | E. W. | 29F | 7 | + | 20 | + | 0 | 0 | 0 | 1138 | 115 |
| 25 | L. W. | 28F | 6 | 0 | 20 | + | + | + | 0 | 342 | 130 |
| 26 | G. Z. | 39M | 7 | + | 25 | + | 0 | + | + | 278 | 98 |
| Average | | | 5 | – | 27 | – | – | – | – | – | – |
| Per Cent of Series | | | – | 85 | 96 | 88 | 27 | 27 | 54 | 76‡ | 20‡ |

@ Data unavailable.
+ indicates yes.
0 indicates no.
*Local laboratory designates 300 Somogyi units as upper limit of normal range.
†Weight gain recorded in pounds when specifically known.
‡Per cent of cases in which data were available.
§Average duct size was 6.3 mm. among those with abnormal ducts.

incident to an untreated abscessed tooth. Her preoperative glucose tolerance test had shown a flat response between 400 and 650 mg. of blood sugar.

*Complications.*—Table II summarizes the operative complications. Six patients had one complication each, and a seventh patient had 3. This latter patient had had 3 previous operations, including gastric resection for duodenitis,

PANCREATITIS TREATED BY PANCREATICOJEJUNOSTOMY

| PREVIOUS SURGERY | | | OPERATIVE FINDINGS | | RESULTS | | | |
|---|---|---|---|---|---|---|---|---|
| OPERATIONS | G.B. | SPHINCTEROTOMY | PANCR. DUCT DIAM. (MM.) | DUCT OBSTRUCT. X-RAY OR PRESS. | MONTHS SINCE OP. | FREE OF PAIN | WEIGHT GAIN† | REMARKS |
| 2 | 0 | 0 | 8 | + | 13 | + | 25 | |
| 1 | 0 | 0 | 3 | 0 | 6 | 0 | + | Pain recurred at 2 mo.; still drinking heavily |
| 2 | + | 0 | 7 | + | 15 | + | 20 | |
| 1 | 0 | 0 | 8 | + | 13 | 0 | + | Pain recurred at 3 mo.; still drinking heavily |
| 7 | 0 | 0 | 9 | + | 23 | + | + | |
| 1 | 0 | 0 | 4 | + | 42 | + | + | |
| 1 | 0 | + | 2 | @ | 5 | + | + | |
| 2 | 0 | 0 | 2 | + | 26 | + | + | |
| 2 | + | 0 | 3 | 0 | 8 | + | + | |
| none | 0 | 0 | 4 | + | 9 | + | + | |
| 1 | 0 | 0 | 8 | + | 36 | + | 21 | |
| 2 | 0 | 0 | 7 | + | 20 | + | 35 | |
| 2 | + | 0 | 3 | 0 | 14 | + | + | |
| 2 | 0 | + | 8 | + | 10 | 0 | + | Prisoner; pain recurred within the month; minimal response to splanchnicectomy |
| 1 | 0 | 0 | 8 | @ | 11 | 0 | + | Pain recurred with severe tonsillitis at 5 mo.; well since |
| none | 0 | 0 | 4 | @ | 1 | + | + | |
| 3 | + | 0 | 4 | + | 13 | + | 8 | |
| none | 0 | 0 | 7 | + | 36 | + | 35 | |
| 2 | + | + | 3 | + | 18 | + | 20 | |
| 1 | 0 | 0 | 8 | + | 7 | 0 | 15 | Pain recurred at 3 mo.; still drinking heavily |
| 4 | 0 | 0 | 4 | @ | 2 | + | + | |
| none | 0 | 0 | 6 | @ | 14 | + | + | |
| none | 0 | 0 | 6 | + | 29 | + | 30 | Developed far-advanced pulm. tbc 18 mo. post-op.; responding nicely |
| 3 | + | + | 4 | @ | 6 | + | + | |
| 4 | + | + | 4 | 0 | 3 | + | + | Died 3 mo. after operation with diabetic acidosis and tooth abscess |
| none | 0 | 0 | 5 | 0 | 9 | + | + | |
| 1.7 | – | – | – | – | – | – | – | |
| 77 | 27 | 19 | 5.3§ | 75‡ | – | 81 | 100 | |

and it was necessary to tailor the pancreaticojejunostomy in terms of a long-limbed antecolic gastrojejunostomy. This was accomplished by dividing the proximal limb of the gastroenterostomy at the ligament of Treitz, implanting the cut end of the fourth part of the duodenum into the side of the proximal limb, the cut end of which was sutured end-to-end to the transected pancreas. A 30 cm. blind loop was still achieved, and biliary and pancreatic juice still entered the jejunum proximal to the gastroenterostomy. On the night of operation, continued hemorrhage from the transected pancreas required re-operation for control, and 9 days later lysis of adhesions was necessary for intestinal obstruction. A left subphrenic abscess required drainage on the twenty-ninth postoperative day.

TABLE II. OPERATIVE COMPLICATIONS

| CASE NO. | INTESTINAL OBSTRUCTION | SUBPHRENIC ABSCESS | HEMORRHAGE | WOUND | | |
|---|---|---|---|---|---|---|
| | | | | INFECTION | HEMATOMA | OTHER |
| 2 | x | | | | | |
| 3 | | x | | | | |
| 7 | | | | | x | |
| 8 | | | | | | x |
| 13 | x | x | x | | | |
| 14 | | | | | | x |
| 24 | | | | x | | |
| Total | 2 | 2 | 1 | 1 | 1 | 2 |

There was one other instance of mechanical intestinal obstruction, also in a patient previously operated upon 3 times, and one other subphrenic abscess. The remaining 4 complications involved the abdominal wound; one had infection, another a hematoma, and 2 had painful wire sutures which required removal later.

*Relief of Pain.*—During the follow-up period 80 per cent of the patients had complete relief of pain. Of the remaining 20 per cent pain recurred within the first 3 months after operation, with one exception. This patient, 5 months after operation, developed abdominal pain and elevation of serum amylase coincident to severe tonsillitis and pharyngitis, requiring hospitalization. However, she has remained free of pain since that episode.

Eliminating the patient who died of diabetic acidosis 3 months postoperatively, 20 patients have remained free of pain up to 3 years following pancreaticojejunostomy. Of the 4 patients who developed recurrence of abdominal pain within 1 to 3 months of operation, 3 had immediately reverted to severe alcoholism, and the other recurred after imprisonment for armed robbery.

*Nutrition.*—Even more striking than the relief of pain was the change in the general nutritional status of all patients. Within a few days following pancreaticojejunostomy, resumption of normal appetite, caloric intake, and feeling of well-being were evident. Weight gain was observed in every patient—as much as 16 Kg. in some cases. There was a positive correlation between the degree of weight gain and the amount of preoperative weight loss. This was equally true in those patients who developed a recurrence of abdominal pain.

*Demeanor.*—There was a striking improvement in the outlook and demeanor of all patients. Impartial observers, who had been associated with the patients before operation, were quick to note the subjective and objective change in attitude. Again, this was evident not only in those patients who were pain free, but also in those who developed recurrent pain. The significance of this observation is not known.

*Glucose Tolerance.*—There was no improvement in glucose tolerance following relief of the pancreatitis among those patients who were diabetic before operation. Of greater importance, however, is the fact that no patient developed diabetes after operation who had not shown preoperative evidence of impaired glucose tolerance. This seems particularly significant since the concentration of islets of Langerhans is greatest in the tail of the pancreas.

*Drug Addiction.*—Four patients were addicted to narcotics before operation. All 4 were successfully withdrawn from the habit within the first 2 weeks of operation. None have relapsed.

## CONCLUSIONS

1. By means of rigid criteria in patients with chronic pancreatitis, it was possible to delineate those with incomplete obstruction of the pancreatic duct. Cases of pancreatitis coexistent with diseases of the biliary or intestinal tract were not included in this study group.

2. Twenty-six patients met the criteria of pancreatic duct obstruction and were subjected to pancreatic duct exploration and decompression by pancreaticojejunostomy.

3. The characteristics of the disease and the operative findings are described.

4. Among the 25 patients followed for a period up to 3 years, 20 have remained free of abdominal pain.

5. All patients gained weight and felt improved, irrespective of elimination of abdominal pain.

6. Four patients with drug addiction were cured of their addiction.

7. In selected patients, this form of therapy may be of considerable assistance in the management of chronic pancreatitis.

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# Reappraisal

CONDUCTED BY CLARENCE DENNIS, M.D. ASSISTED BY ALFRED HURWITZ, M.D.

## MANAGEMENT OF PATIENTS WITH MASS HEMORRHAGE FROM ESOPHAGEAL VARICES AND CIRRHOSIS OF THE LIVER

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THE problem of saving the lives of patients with cirrhosis of the liver who bleed from varices in the esophagus is a very difficult one because in addition to hemorrhage the factor of a poorly functioning liver raises other obstacles. In fact, a low mortality rate can never be achieved in this group of patients whatever the treatment may be. Nevertheless, we must continuously work to improve the situation, trying one approach after another.

When a patient with cirrhosis of the liver bleeds into the gastrointestinal tract, he is actually the victim of a forced feeding of a large amount of easily digestible protein (blood). The ammonia formed and absorbed in the course of this tremendous meal of blood is too large for an impaired liver to metabolize. A rise in the level of venous blood ammonia follows massive hemorrhage in cases of cirrhosis rather than a high value for nonprotein nitrogen which is the case in hemorrhage from gastroduodenal ulcer in patients who have normal livers. An excessive amount of ammonia in the blood is toxic. It is important, therefore, that hemorrhage can be stopped promptly in patients with cirrhosis because of this factor of ammonia intoxication which leads to a variety of encephalopathies and finally coma. In other words, adequate replacement of blood and the maintenance of a normotensive state in the hope that hemorrhage will cease is not sufficient, nor is it adequate therapy in the bleeding cirrhotic patient. These patients continue to bleed and may die of poisoning by their own blood, so to speak. The mortality rate was 66 per cent in one series of patients at the Albany Hospital.[4] Approximately one-third of the patients who succumbed died in coma. No patient who went into coma survived.

It occurred to us in reviewing these findings that more careful attention to the accuracy of tamponade treatment and ammonia intoxication might lower this high mortality significantly. Accordingly, we instituted what we called for purposes of emphasis a "3-point program," which is as follows: (1) stop the hemorrhage by tamponade, (2) evacuate blood from the gastrointestinal tract by enemata and physics, and (3) repair and detoxify the patient.

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Hemorrhage from varices can be stopped by the Sengstaken-Blakemore tube tamponade method. It should be used early and in all cases suspected of bleeding from varices. It is also a good diagnostic instrument in that, if it stops the bleeding, the evidence is good that the site is at the esophagogastric junction and probably from varices. All too often, tamponade is instituted late, largely because shock is controlled in moderate bleeders by transfusions of blood. Also, too often hemorrhage is believed to have stopped when the blood pressure is stabilized. Tamponade must be looked upon as a means of preventing coma as well as shock from blood loss if we are to appreciate the importance of its employment early in the bleeding episode.

It follows quite naturally that efforts should be made to evacuate the existing noxious material (blood) from the bowel. To stimulate the gastrointestinal tract during bleeding seems heretical and perhaps is so in patients bleeding from an ulcer, but it has no untoward effect during tamponade since the bleeding is controlled. We use frequent doses of milk of magnesia (hourly or every 2 hours) administered through the gastric tube. Enemas are also given.

In regard to the third factor in treatment, namely, reparative and detoxifying therapy, the use of blood, plasma, vitamins (especially K), and the control of fluid and electrolytes, no special mention is needed here although this part of the treatment is important. One important consideration in electrolytes is the limitation of sodium intake when there is evidence of water retention. The control of ammonia intoxication is a new endeavor, however. Values for blood ammonia should be taken on admission and twice daily. We consider any ammonia value above 100 mcg. per cent to be abnormal. A rise in the value for blood ammonia is indicative of impaired liver function, on the one hand, and it also gives some indication of the size of the hemorrhage. Continued rise in the ammonia is a poor prognostic sign and coma follows on its heels. Formerly, we thought of this coma as the direct result of liver failure with the implication that there was a progressively diminished function of the liver. Actually, the liver is unchanged and is functioning as well as it did prior to hemorrhage in many cases exhibiting coma. Coma in the usual hemorrhage is in reality of exogenous origin, the result of blood in the gastrointestinal tract. Fortunately, coma of exogenous origin can be treated.[2] Sodium glutamate administration is of value in reducing blood ammonia but its effect is quantitative and, therefore, transitory if bleeding continues. Nevertheless, it is of value in controlling ammonia intoxication. Twenty grams in one liter of 5 per cent dextrose and water are given at one time and repeated as indicated. We have used the artificial kidney and dialyzed substantial amounts of ammonia out of patients' blood. This technique is of special value in patients with very high values for ammonia. Finally, however, keeping the patient alive and stopping the hemorrhage are the most important steps in treating coma. If the source of abnormal ammonia production is cut off, the high blood ammonia will ultimately decrease and intoxication will be

relieved. Sterilization of the bowel by the administration of a wide spectrum antibiotic is indicated also since this has been shown to reduce ammonia production in the intestine.

It must be said that hepatic coma of the type caused by a liver failing in its function because of increasing degenerative changes can and does occur in some cases. This is often seen late in hemorrhage and in terminal cases. The control of ammonia intoxication has little effect in the presence of this eventuality.

After applying this 3-point program to the management of our patients, we found that the mortality rate has improved but not to the degree we had hoped. We have been able to keep patients alive much longer by medical measures. Patients have been brought out of coma, sometimes more than once. The ultimate deterrent to a totally successful outcome of the episode of hemorrhage has been recurrence of bleeding after release of the tamponade. At this stage, many patients are unable to withstand a second bleeding. Some have pulmonary complications; others begin to have true liver failure, the result of degenerative liver changes. The technique of compression of the varices, therefore, must be looked upon as a good temporary measure but inadequate to the task at hand. It does not stop bleeding for any length of time in a sufficient number of patients, certainly not long enough for them to be prepared for the definitive portacaval shunt. Therefore, we believe that some more substantial measure should be used to stop hemorrhage. There are two worthy procedures. Ligation of the varices as a temporary means of controlling hemorrhage seems to offer promise. The performance of portacaval shunt as an emergency procedure is the alternative. This latter procedure has one theoretical disadvantage; it does not attack the site of bleeding. Whether it will stop hemorrhage by relieving portal pressure in a reliable manner, we do not know.

Presently, we favor emergency ligation of the esophageal varices to be followed later by a portacaval shunt. The latter must be done as soon as possible, that is, as soon as the patient's condition allows since ligation does not permanently control bleeding. Recurrence of bleeding has been noted 8 weeks after ligation. It is important to perform ligation early in the hemorrhage episode, not exactly as an emergency but as soon as the patient is stabilized. This means that his bleeding is controlled by tamponade, his blood losses are replaced, and some evacuation of blood from the gastrointestinal tract has been effected. Ligation is done, therefore, from 24 to 72 hours after admission. Patients who would have been good candidates for shunt procedure, as judged by their physical status and liver function, had they not bled are good candidates for emergency ligation. It is our belief that mortality can be reduced in this group by early ligation. Difficulties arise in deciding about operation in poor risk patients, particularly those who come late to the surgeon's attention and have very poor liver function with visible jaundice and ascites. Our experience has not been good in these patients, and presently, we have taken the stand that it may be impossible to try to salvage them by surgery. On the other hand, since the outlook is usually hopeless without stopping the hemorrhage, there is

a good argument that these patients should not be excluded from consideration for ligation. We have not decided this point. Actually, we have operated upon more patients in this group than the better one.

Ligation of esophageal varices was first done by the transthoracic route. We prefer the transabdominal route for several reasons.[3] There is a higher incidence of gastroduodenal ulcer disease among cirrhotic patients, and some of these patients are actually bleeding from ulcers rather than varices. The abdominal approach allows a more accurate diagnosis of the source of bleeding in that the stomach and duodenum can be thoroughly inspected.[1] More than this, if a gastric or duodenal ulcer is found to be present, it can be resected. The abdominal approach eliminates, therefore, the dilemma of uncertainty of the diagnosis. If there is no ulcerating gastroduodenal lesion, the esophagus and upper stomach can be opened longitudinally and the varices oversewed. The actual bleeding point will not be found after tamponade, but oversewing the varices in groups insures against further bleeding. Simple longitudinal closure of the stomach and esophagus is then carried out. A second reason for preferring the abdominal approach is that it is probably better tolerated by the patient since pulmonary function is not disturbed. Six patients have had transabdominal ligation with 3 deaths. It is impossible to offer a predictable mortality rate for such a procedure since so much depends upon the type of patient subjected to the operation. A combination of attention to details of medical treatment and employing ligation of varices in selected cases, therefore, seems to be a reasonable approach to this whole problem. It should be emphasized that the 3 points of the nonoperative treatment program are very important and must be applied to the management of operated as well as nonoperated patients. Our present mortality rate is 59 per cent in 44 patients but has been reduced to 39 per cent among the last 15 patients. We believe that a good trial of the operation of ligation of varices performed early is needed and justified. It remains for the internist to appreciate that there is a surgical aspect to treating bleeding in cirrhotic patients and, therefore, to consult the surgeon as soon as these patients come under his care.

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# Book Reviews

CONDUCTED BY J. GARROTT ALLEN, M. D.

**Les icteres par retention, diagnostic medico-chirurgical.** J. Caroli, Paris, 1956, Masson & Cie. Pp. 448, 308 ills.

*The Diagnosis of Regurgitation Jaundice* is essentially a review of the diagnostic methods employed by the author and his associates of the St. Antoine Hospital in Paris for the work-up of 341 cases of regurgitation jaundice observed by them during the years 1951, 1952, and 1953.

The outline of the book follows the successive steps from clinical work-up to surgical exploration, leading to the final diagnosis. On the basis of the history and physical findings alone, a definite diagnosis was made in 70 per cent of their cases. It is interesting to note that in 40 per cent of their cases of infectious hepatitis they found diagnostic signs such as preicteric rheumatism, migraine, or urticaria.

On the basis of information derived from biochemical tests of liver function, a diagnosis was possible in an additional 15 per cent in which clinical examination alone had been inconclusive. The tests found to be most useful were the thymol turbidity test, the cephalin flocculation test, the total cholesterol level, galactosuria, and the plasma protein levels.

Various radiologic techniques contributing to the diagnosis of regurgitation jaundice, such as simple flat plate of the right upper quadrant, barium outline of the duodenum, cholecystogram, intravenous cholangiogram, and portogram are described.

A particularly interesting chapter is devoted to the technique of laparoscopy as applied to the diagnosis of regurgitation jaundice. In certain cases of jaundice, the origin of which the usual clinical and laboratory methods were unable to elucidate, laparoscopy instead of laparotomy was helpful. This was achieved either by observing gross changes in the appearance of the liver (color photography), by taking biopsies under laparoscopic control (much preferable to a blind liver biopsy), or by injecting the biliary tree, again under laparoscopic control (method of Royer).

In our opinion, the most valuable section of the book, at least for the American reader, is that dealing with the method of operative cholangiography used by Dr. Caroli. The salient points of this method are injection of the biliary tree under constant manometric control and under physiologic pressures, fluoroscopic control, and serial films. The biliary tree is gradually opacified by the contrast media and not flooded. This is the only way in which the subtle alterations of the bile tract can be brought into evidence. It becomes apparent that an operative cholangiogram performed with a poor technique is worthless. It also seems apparent that by this method and with a certain amount of experience in its use the surgeon may avail himself of much valuable information. The illustrations in this section are very abundant and of excellent quality. This material should by all means be read by those interested in this controversial subject.

The book is written in a very clear, concise, and pleasant style. This along with the profuse illustrations should make its contents available to those with even superficial knowledge of French.

Dr. Caroli is to be congratulated for this very valuable contribution.

—Jessie N. Bollman

**The Dental Treatment of Maxillo-Facial Injuries.** Sir William Kelsey Fry and Terence Ward. Springfield, Ill., 1956, Charles C Thomas. Pp. 372, 383 ills. $9.50.

This book, produced by two eminently qualified British dental surgeons, is the second edition of a highly useful compendium in the field of maxillo-facial injuries. While the first edition, printed in 1942 in England, was a smaller volume, a supplement was prepared soon after to amplify and illustrate more completely the various clinical applications of the principles described in the parent publication.

The present volume provided the opportunity to bring together the material in the first edition as well as the supplement including a chapter entitled "Fractures of the Middle Third of the Face" by Sir Archibald McIndoe. In addition, the advent of new methods, drugs, and materials has permitted the present volume to be brought up to date in these vital matters including certain emendations. Originally this book was the collaborative effort of four authors who were all part of the Maxillo-Facial Unit at East Grinstead. Since then, however, Shepherd, McLeod, and Parfitt have left the field, the latter coming to the United States. It was the decision of this team that the present volume be carried on by the senior of the original authors in collaboration with Terence Ward, of the Queen Victoria Hospital in East Grinstead.

Most of the work in the area of oral surgery was brought to its present form during World War II. Some of the maxillo-facial centers set up during that period in England have been converted to civilian use mainly for treatment of automobile injuries. The East Grinstead center is the foremost unit of its kind in the British Commonwealth.

As a whole the present volume is based on sound common sense and an intimate comprehension of general surgical principles. It is found to be concisely and clearly written with excellent illustrations and diagrams. The book in its lucid form is essentially practical in its mode of presentation. Yet the authors never lose sight of the fact that pathologic processes underlie all surgical treatment. Hence the chapter on surgical pathology is especially well presented with its 13 color plates. Other chapters take into consideration anatomic aspects of the injuries, types of fractures, clinical diagnosis, radiology, surgery on soft and hard tissues, sulfonamide and antibiotic therapy, reduction and fixation, fractures of the middle third of the face, and complications. Chapter XII on technique including impression-taking and splinting as well as Chapter XIII on initial and preliminary hospital treatment are both excellent and provide factual information with a minimum of discussion. The chapter on loss of tissue (XV), while presenting many case reports, some from World War I, which make interesting reading, might have been more elaborately illustrated relative to facial and oral prosthesis.

All in all the book with its 16 chapters is a meritorious achievement and should retain for many years its eminence in oral surgery literature.

—Frank J. Orland

**Principles and Methods of Sterilization.** John S. Perkins. Springfield, Ill., 1956, Charles C Thomas. Pp. 340. $8.00.

The author presents a clear concept of the basic principles of sterilization. The wide variety of sterilizers in current hospital use poses problems in correct maintenance, loading, and operation. The book will answer many of the questions which arise during the sterilization cycle for those interested in this field. It will be especially appreciated by supervisors who have the responsibility of training personnel in proper techniques of bacteriologic sterilization.

The text deals with steam and gas sterilization. Steam techniques are discussed in somewhat greater detail, although gas affords very desirable potentialities which should be explored further and developed more fully.

The use of ethylene oxide is an approach described for sterilizing heat-sensitive articles such as those composed of plastic, rubber, and leather. This particular gas may

not be the ultimate answer, but perhaps it alone or in combination with other gases may open new paths in efficiency and economy.

Those individuals currently using steam techniques will be very much interested in the author's presentation of procedures which he considered essential to safety.

The principles and minimum standards are lucidly set forth. As an aid in reaching these minimum standards, the reasons for failures are discussed with the admonition that each steam pressure unit should be subject to routine periodic evaluation by means of culture tests.

Essential for effective sterilization is the standardization of the entire cycle. These include the selection of the material for sterilization, the methods of packing and loading the unit, to the withdrawal of the finished product. The adherence to such a routine, the author feels, is the responsibility of the supervisor.

Individuals responsible for the preparation and maintenance of sterilized materials will be very much interested in the following topics:

1. The preparation and sterilization of dressings, dry materials, rubber goods, and surgical instruments are reviewed. Many useful ideas are presented.

2. Probably the widest interest will center upon the chapter dealing with the sterilization of needles and syringes.

3. The planning and organization of a central supply service, a parenteral solution department, and infant feeding formula unit are given attention. Because these divisions have individual problems of specialized sterilization, the discussion is helpful.

The author has achieved in his writings an admirable degree of impartiality in a difficult field. Where there are existing controversies over technique, he has dealt fully with the pros and cons. Further than this, he permits reader evaluation through the inclusion of a rather complete bibliography.

The discussion of the development of sterilization from the pre-Christian Era is fascinating, first, from the standpoint of the information presented. Second, in the hands of a skillful supervisor, it can be used for the motivation of operating personnel by dramatizing the age-old need for asepsis in medicine.

The book warrants serious consideration for a spot on the shelf of any supervisor responsible for the maintenance of sterilized materials and the training of personnel in techniques pertinent thereto.

—Carolyn Sykes Scott

**L'Arresto del cuore in chirurgia.** C. Lacerenza. Firenze, 1956, Casa Editrice Macri. In Italian. Cardiac Arrest in Surgery. Preface by Dr. Professor Dino Pampari. Pp. 98, 24 ills., 3 color plates. 3500 Lira.

This monograph presents a review in small compass of the salient factors that form our present knowledge of the diagnosis and treatment of cardiac arrest. The volume is a valuable presentation not only to the surgeon, but also to the anesthesiologist, the physician, and indeed to all members of the medical fraternity in active practice. There is a carefully compiled bibliography, with notable evidence that most of the past and current study in this field has been by American authorship and research.

The introductory chapters consider the history of the subject dating from the earliest case recorded of death ascribed to cardiac arrest (Hannah Greener, Jan. 28, 1848) following anesthesia with chloroform, until the success of Beck, in 1947, who successfully defibrillated a human heart through the medium of electric shock therapy.

The author then goes on to point out the great discord in data regarding the frequency of cardiac arrest as presented by different authors. He reviews the physiopathology of the myocardium and reviews in some detail the causes of cardiac arrest. These he divides into three groups: (1) factors inherent in the condition of the patient, (2) factors inherent in the anesthesia, and (3) factors inherent in the operative intervention.

Other chapters consider the frequency and role of ventricular fibrillation with cardiac arrest in surgery, the diagnosis of the condition in the human patient, and the various methods of treatment—unimanual cardiac massage, bimanual cardiac massage, massage through the diaphragm, and the treatment of ventricular fibrillation using the Beck-Rand shock type defibrillator.

The author's concluding chapter cites some personal cases with their histories and summarizes the results of the treatment of cardiac arrest. Notwithstanding the meticulously compiled bibliography, a system of line references and enumerations would have aided the reader considerably. The book is to be recommended particularly where the original literature is not readily available.

The importance of a knowledge of cardiac arrest to all physicians, not alone to surgeons, has recently been cited in the Lancet (**271**: 1201, 1956, and **272**: 47, 1957). Milstein with concise clarity there indicates "the time has come when all, including physicians and general surgeons, who carry out any procedure on a patient which may cause cardiac arrest should be capable of dealing with the situation by thoracotomy and general massage." Beck, C. S. (In Henry Ford Hosp. Internat. Symposium on Cardiovascular Surgery, Philadelphia, 1955, p. 404) has not overemphasized the problem when he states, "I don't think we are doing the right thing for our patients unless we have a knowledge of resuscitation procedures. . . . There is no excuse, it seems to me, for a surgeon not knowing how to resuscitate a heart."

—Stacey B. Day

**Proceedings of the Third National Cancer Conference.** Detroit, Mich., June 4-6, 1956. Sponsored by American Cancer Society, Inc., and National Cancer Institute, U. S. Public Health Service. Philadelphia, 1957, J. B. Lippincott Company. Pp. 961. $9.00.

This book is the best source of information on the clinical problem of cancer yet published. Its title does not convey the enormous amount of clinical and experimental data covered, nor the fact that the book contains numerous and excellent articles by experts in the field. In this single volume are contained the most recently available data and results by most of the major students of neoplastic disease in this country and many from abroad.

The subjects covered include cancer of the breast, the prostate, the lung, head and neck, female genital tract, gastrointestinal tract, leukemias and lymphomas, and chemotherapy. Special lectures are presented on epidemiology, radiation neoplasia, virus etiology, chemical effects of cancer, factors influencing curability, and the measurement of morbidity. Each of these subjects is covered well and by men competent in the clinical and/or the experimental aspects of the particular organ or cancer being discussed. Moreover, discussions of each paper are presented which clarify or point out divergent opinions in a most useful manner.

The major criticism I wish to point out has to do with the need for the adoption of some conformity when reporting clinical experience. It is therefore a criticism directed toward methods of presentation and not the book per se which of course must confine its coverage to the conference data as given by the various authors. Albeit, conformity may be difficult, but it does not appear to present an insurmountable problem nor to penalize the authors. For example, the reports of Dahl-Iverson and of Urban would be more meaningful if their central theme on the benefits of the extended radical mastectomy had at least some tables wherein their respective data could be directly compared. Even more useful would have been the results from radiation compiled in a common framework of tables. To some extent this type of comparison was achieved in the "Symposium on End Results in the Treatment of Cancer" in this book, but here again it is not possible to extract certain data from the Tables of End Results so that the reader can rework the data in some other manner should he choose to do so. It is to McWhirter's credit that in

the presentation of his work elsewhere, he simplified his stages of the disease as well as his results. His stages, however, are less meaningful than they might have been had he depended upon pathologic demontration instead of clinical impression.

Nonetheless, the initial premise still stands: there is no more useful source of information available anywhere to any physician treating cancer or counseling patients about cancer. This book is excellently printed, illustrated, clear, and concise. All who took part in this Third National Cancer Conference did so with distinction.

—J. Garrott Allen

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## Announcement

The Pittsburgh Surgical Society sponsored its third Annual Lecture on Monday, May 27, 1957.

The speaker on this occasion was Dr. Bronson Ray, Professor of Neurosurgery, Cornell University Medical School, New York, N. Y. The title of his address was "Hypophysectomy in the Treatment of Advanced Mammary Cancer."

Dr. Ray was the recipient of the Society's Silver Plaque at a dinner preceding the lecture. Previous recipients of the Silver Plaque have been Dr. Charles Mayo (1955), and Dr. Evarts A. Graham (1956).

## Calendar of Surgical Meetings

### 1957

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 11-13, 1957, The Cloister, Sea Island, Ga. Deadline for papers, Aug. 15, 1957. Secretary, Dr. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, N. C. Attendance at meetings by invitation only.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 31, Nov. 1 and 2, 1957, The Homestead, Hot Springs, Va. Deadline for papers, Aug. 1, 1957. Secretary, James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 28-29, 1957, Park-Sheraton Hotel, New York City, N. Y. Participation by invitation only.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 14-18, Convention Hall, Atlantic City, N. J. Secretary of the College, Michael L. Mason, 154 E. Erie St., Chicago 11, Ill.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* June 3-7, 1957, Coliseum, New York, N. Y. Deadline for papers, Dec. 15, 1956. *Clinical Meeting,* Dec. 3-6, 1957, Auditorium, Philadelphia, Pa. Deadline for papers, July 15, 1957. Secretary, American Medical Association, George F. Lull, M.D.; Secretary, Council on Scientific Assembly, Thomas G. Hull, M.D.; address of both, 535 North Dearborn Street, Chicago 10, Ill.

INTERNATIONAL SOCIETY OF SURGERY. *Seventeenth Congress,* Oct. 20-27, 1957, City University Medical School, Mexico City. Details of hotel accommodations and reservations are being handled by "Mexamericana," Paseo de la Reforma 44, Mexico, I. D. F.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 4 and 5, 1957, Mount Washington Hotel, Burton Woods, N. H. Deadline for papers, June 1, 1957. Secretary, Richard Warren, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

PAN-PACIFIC SURGICAL ASSOCIATION. *Seventh Congress,* Nov. 14-22, 1957. Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

THE SOCIETY FOR VASCULAR SURGERY. *Annual Meeting,* June 2, 1957, Hotel Biltmore, New York, N. Y. Secretary, Henry Swan, M.D., 4200 E. 9th Avenue, Denver, Colo.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 10-12, 1957, Greenbrier Hotel, White Sulphur Springs, W. Va. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore 18, Md. Guests are invited by the Secretary at the request of the Membership.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* November 21-23, 1957, Hotel Utah, Salt Lake City, Utah. Deadline for submission of papers, Aug. 15, 1957. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.

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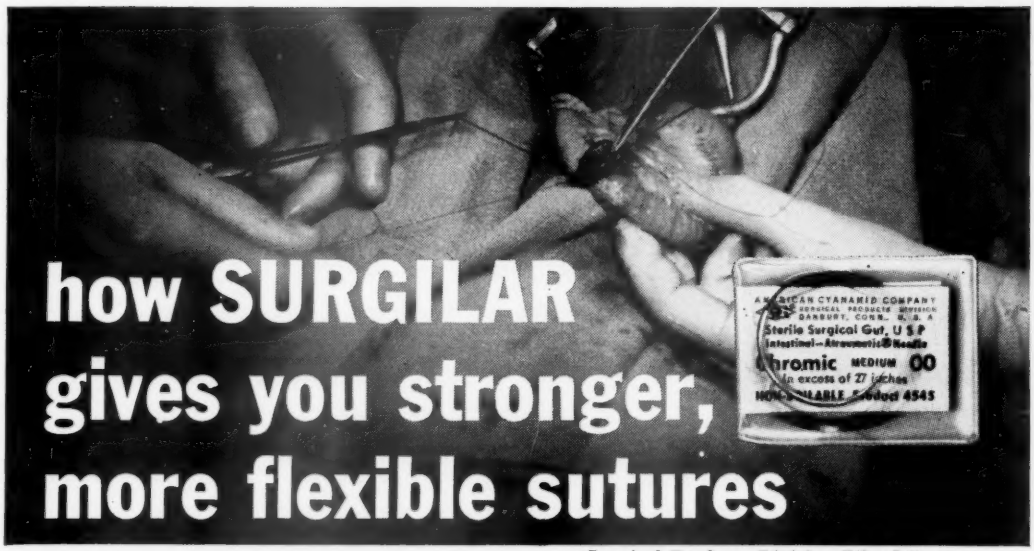


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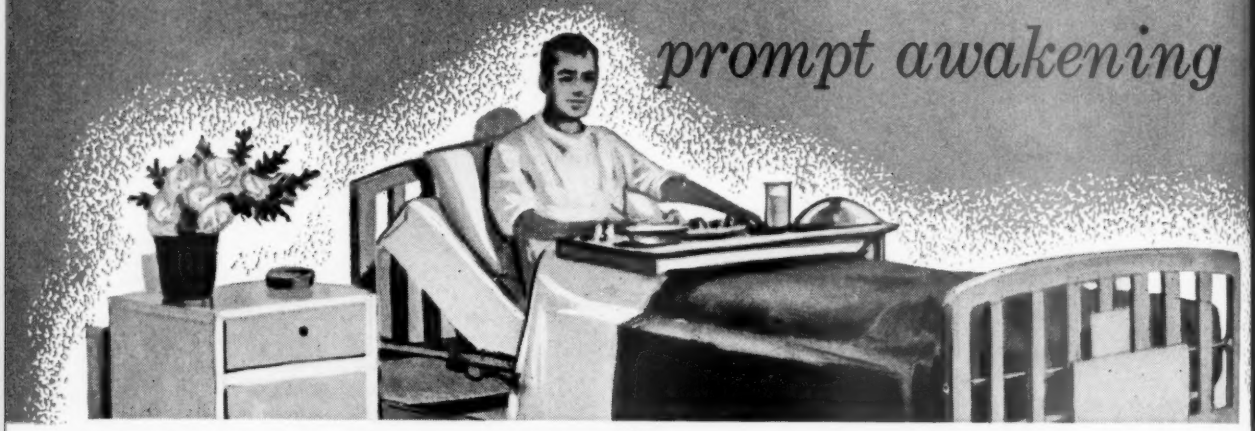

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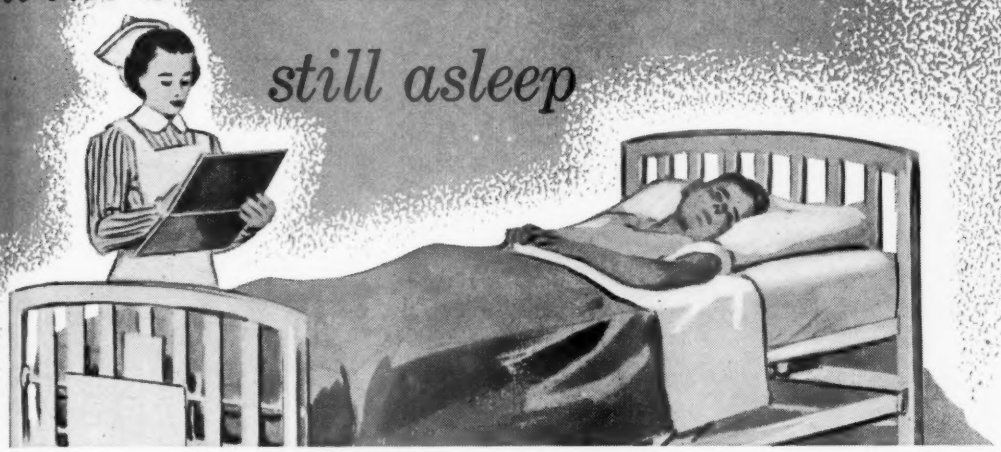

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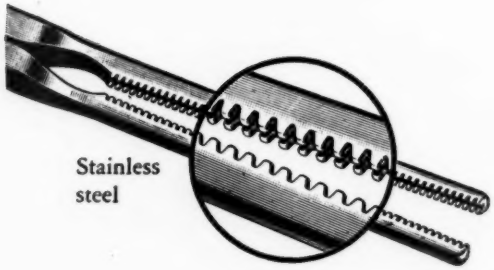


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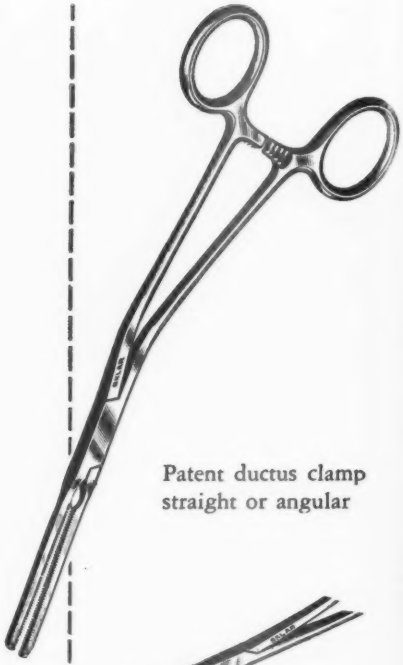
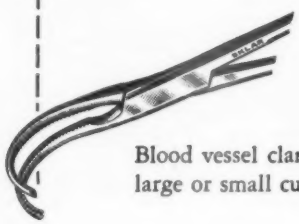


Patent ductus clamp
straight or angular

Satinsky
vena cava clamp



Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular

Bronchus clamp, angular

Bulldog clamp
2", 2½" 3", 3½"

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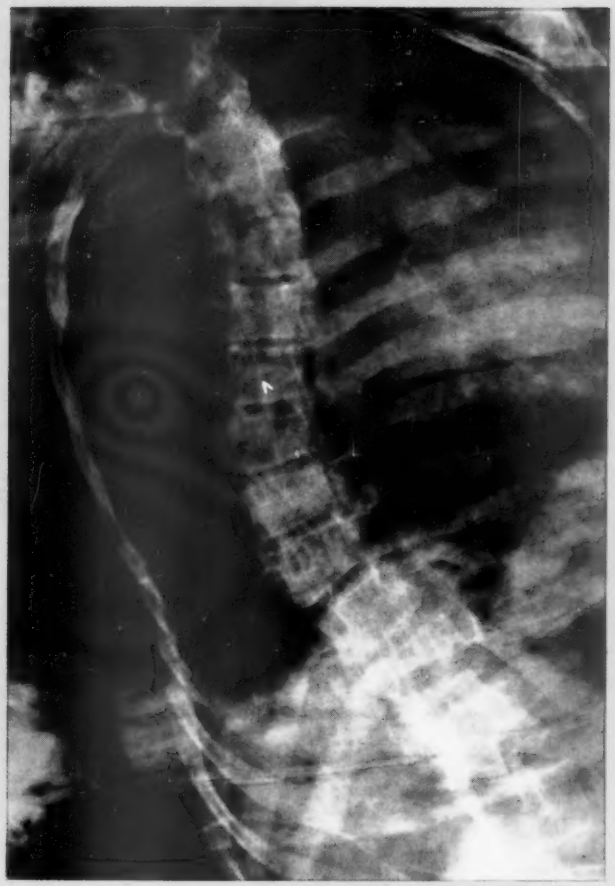

**2.** Postcorrection radiograph with patient in plaster jacket following spinal fusion (top and bottom of the fusion marked by metallic clips).

Right dorsal curve has been corrected in plaster turnbuckle jacket and back is
en exposed through window. Methylene blue tattoo marks identify area of
rtebral column to be fused. *Steps in surgery shown on page following.*

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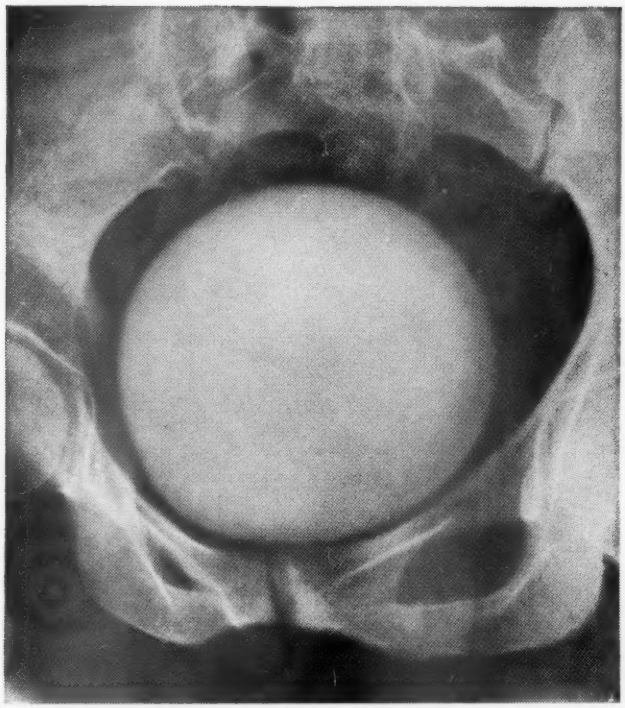
4. Posterior elements of the vertebrae to be fused have been expos by subperiosteal dissection.

5. Interdigitation of bony spicules across the interlaminal spaces h been completed.

6. Raw bony area is reinforced by slivers of cancellous bone obtaine from the bone bank.

7. Incision closed.



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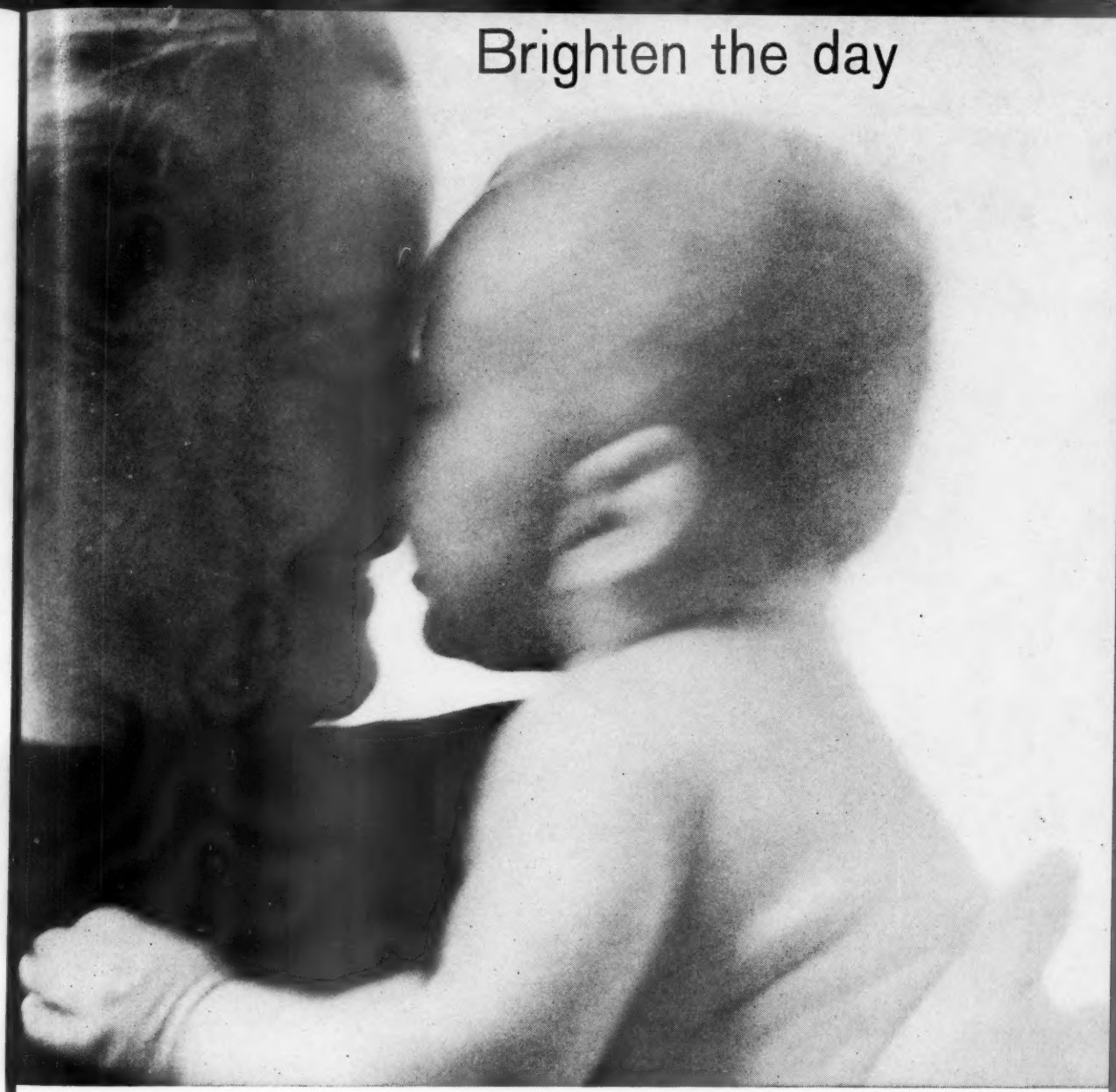


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# OPERATIVE TECHNIC of ANUS, RECTUM, and COLON

*by*

HARRY E. BACON, Professor and Head of Department of Proctology, Temple University Medical School, and STUART T. ROSS, Attending Proctologist, Nassau Hospital, Mineola, New York, and Mercy Hospital, Rockville Center, New York.

301 pages, 403 illustrations. Size: 8½" x 11"
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Surgery of the colon, rectum, and anal canal has spread widely in recent years —but this is the first extensive atlas.

In this atlas the authors give detailed technics for surgical correction of all diseases of the anus, rectum and colon —both in text and pictures.

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Following preliminary chapters on anatomy, preoperative and postoperative care and anesthesia, each operation is considered under the following headings: General description, indications, preparation, position, technic, and postoperative care.

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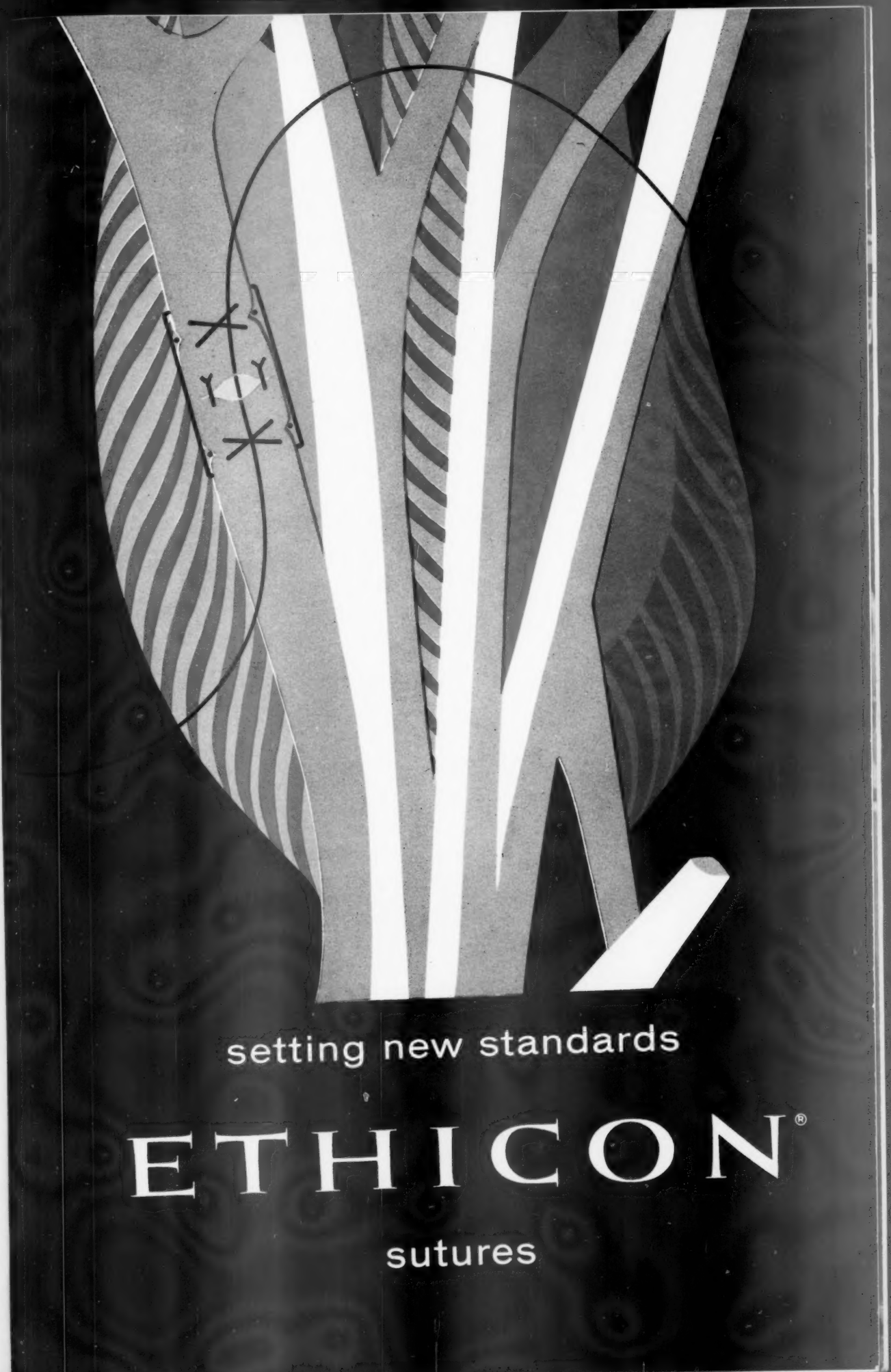
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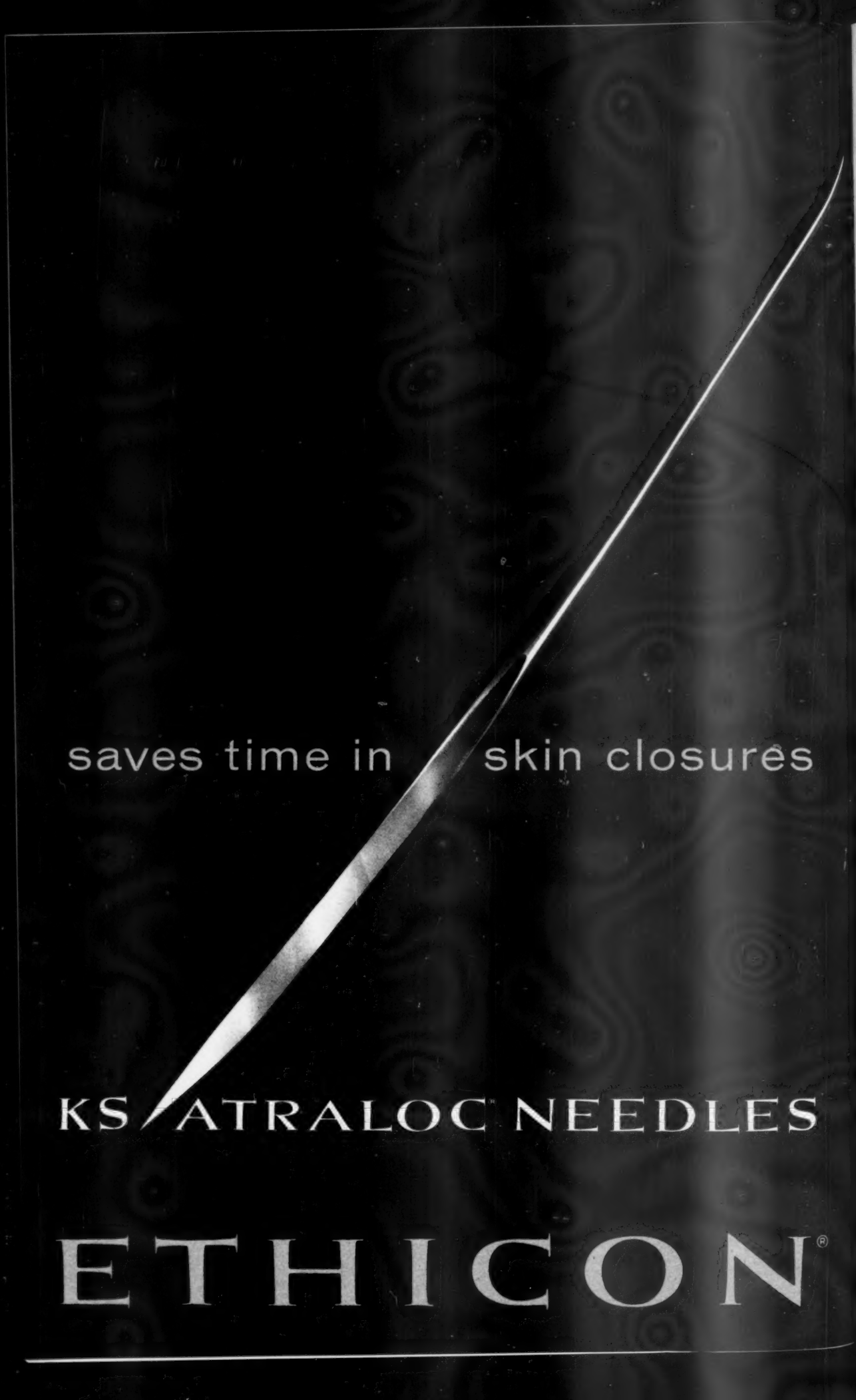
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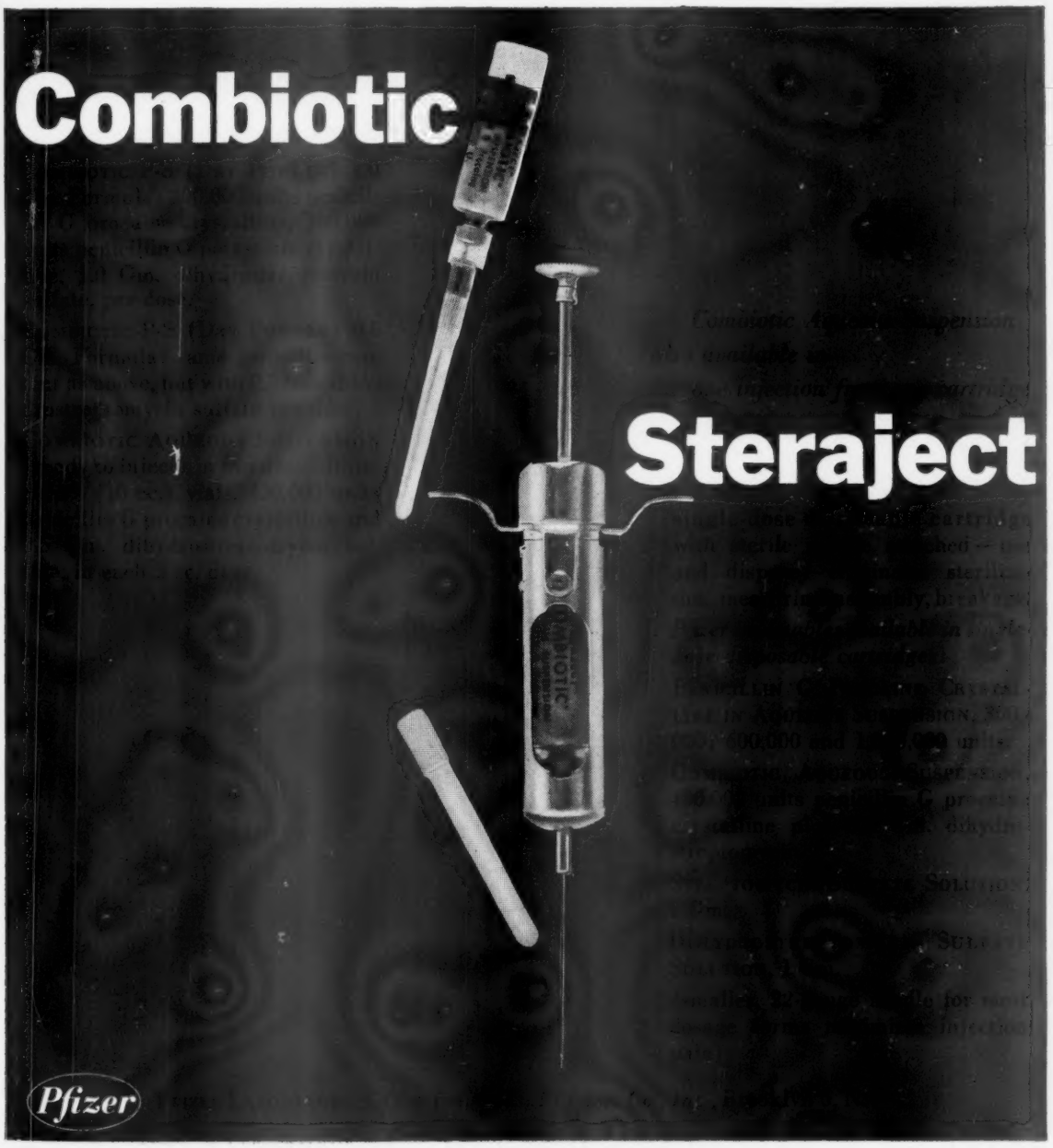

*Gives the Answers To All of Your Shoulder Problems!*

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JAMES E. BATEMAN, M.D., F.R.C.S. (C). Diplomate American Board of Orthopaedic Surgery; Fellow American Academy of Orthopaedic Surgeons; Orthopaedic Consultant, Sunnybrook Hospital, Toronto, Department of Veterans Affairs of Canada; Consultant, Workmen's Compensation Board of Ontario.

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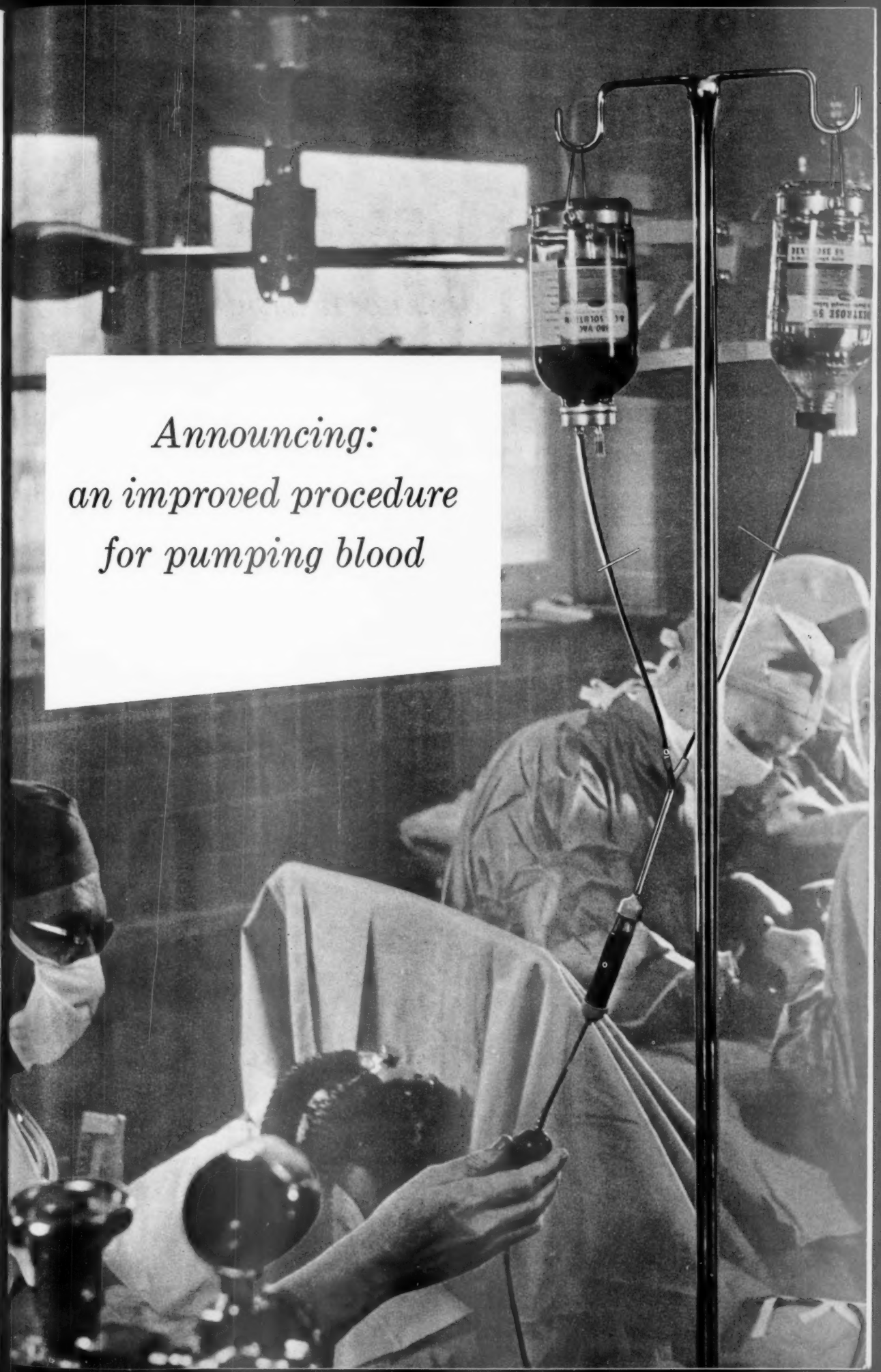
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## A
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